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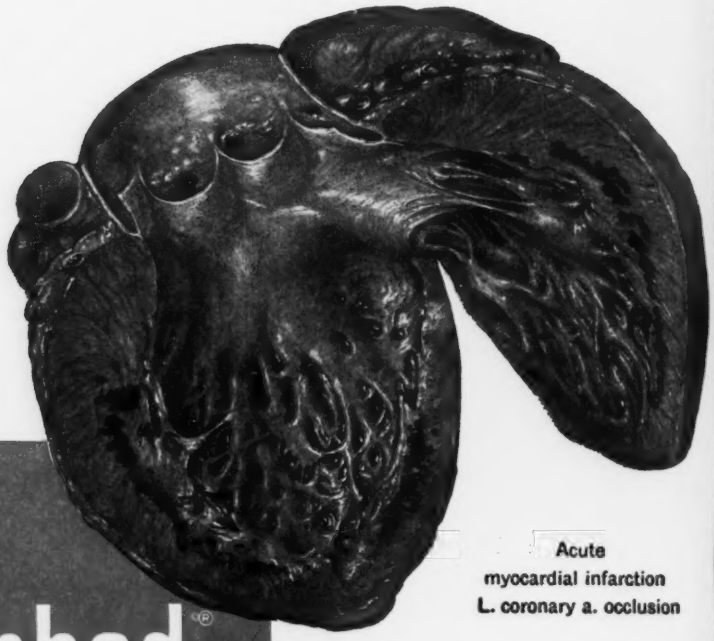

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Atrial Septal Defect

Clinical and Physiologic Response to Complete Closure in Five Patients

By S. Gilbert Blount, Jr., M.D., Henry Swan, M.D., Goffredo Gensini, M.D., and Malcolm C. McCord, M.D.

Complete surgical closure of an atrial septal defect was accomplished under direct vision in five patients. Postoperative catheterization studies demonstrated complete obliteration of the previously existing left-to-right shunt and a reduction of the pulmonary artery blood pressure in all patients. The clinical and hemodynamic status returned to normal limits with but few exceptions.

THE ATRIAL septal defect is one of the most common, if not the commonest, of all congenital heart anomalies.[1, 2] The clinical features of the atrial septal defect have been evaluated more precisely in recent years so that the clinical diagnosis may now be established with reasonable accuracy.[3, 4] However, the differential diagnosis between the atrial septal defect and anomalies of pulmonary venous connections, as a sole defect or together with an atrial septal defect, remains most difficult if not impossible.[5]

The natural history of patients with an atrial septal defect shows wide variation, and it is well recognized that in many patients this defect is compatible with relative longevity and an active life. Nevertheless, the mean duration of life in patients with this defect falls in the middle to late thirties, and many patients die during the early years of life.[6, 7] Large defects may lead to death in early life due to the development of congestive heart failure secondary to the great increase in right ventricular work, while in other patients the development of pulmonary artery hypertension leads to disability and finally death from cardiac decompensation.

Considering the variation in the natural history of this anomaly, and, therefore, realizing that many of these patients will benefit from closure of their atrial septal defects, an attempt was made to determine which patients might be expected to develop pulmonary hypertension. This attempt was made by an evaluation of the clinical status and the data derived from the catheterization of 25 patients considered to have an isolated atrial septal defect.

The present studies also offered the opportunity for the evaluation of certain concepts that have become associated with the atrial septal defect, in particular the presence of mitral stenosis resulting in the entity known as Lutembacher's syndrome.

Five patients were selected for surgical therapy from the group of 25 patients with established atrial septal defects. The main purpose of this paper is to present the clinical and physiologic changes following the complete closure of the atrial septal defect in these five patients.

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Material and Methods

The five patients presented at this time have been selected from a group of 45 patients observed during the past three years in whom a clinical diagnosis of an atrial septal defect was entertained. Twenty-five of these patients have been adequately studied by physiologic methods, verifying the presence of a left-to-right shunt at the atrial level, and thereby strongly suggesting the diagnosis of an uncomplicated atrial septal defect. From this group of 25 patients, five were selected for closure of their atrial septal defects. Cardiac catheterization was performed by the usual technic, with pressures determined by means of Statham strain gauges and a Hathaway recording apparatus. The zero reference point was 10 cm. above the patient's back in adults, and 5 cm. above the back in patients weighing less than 20 Kg. Blood gas determinations were made by the Van Slyke-Neill manometric method,[8] and respiratory gas determinations were carried out according to the Scholander micro technic.[9] The phonocardiogram was obtained by the use of a Cambridge cardioscope and recorded through a Tektronix preamplifier and a Hathaway galvanometer with a frequency response of 1200 cycles per second.

Results

Physiologic Data Evaluated in an Attempt to Select Patients for Surgery

Twenty-five patients with a clinical diagnosis of an atrial septal defect have been evaluated by means of cardiac catheterization. These patients were divided into two groups on the basis of the level of their pulmonary artery blood pressure. This method of division was selected because it is considered that the development of pulmonary hypertension is the major factor leading to progressive disability and death.

The pertinent data obtained by catheterization in these two groups is depicted in table 1. Group A consists of 13 patients with a normal level of the pulmonary artery pressure, and group B is composed of 12 patients with elevated pulmonary artery blood pressure. A mean pulmonary artery pressure of 20 mm. Hg was considered as the upper limit of normal.

Table 1.—*Physiologic Data on 25 Patients with an Atrial Septal Defect. Group A, 13 Patients with Normal Pulmonary Artery Pressure; Group B, 12 Patients with Pulmonary Artery Pressure Elevation*

Group	Age	Pulm. Artery Press. mm. Hg Syst./ Diast.	Pulm. Artery Mean Press. mm. Hg	Pulm. Artery Saturation %	Pulm. Index L./min./ M.²	Total Pulm. Artery Press. Dynes/ sec./ cm.⁻⁵
A	17.6	25/10	15	85.8	13.2	122
B	21.1	63/31	42.0	70.9	8.0	770

It is noted that little difference exists as regards age in groups A and B. In group A the mean age was 17.6 years, while in group B the mean age was 21.1 years. Moreover, the age spectrum was roughly similar in each group. In group A, the normotensive group there were patients aged 50, 47, and 33 years as well as younger patients; while in group B there were also older patients aged 56, 49, 30 years, as well as patients in the younger age group, namely 5, 6 and 7 years. Thus it would not appear that age, as reflecting duration of pulmonary blood flow, in itself is a major factor in the development of pulmonary hypertension. One patient in group A, 47 years of age, had a pulmonary index of 12 liters and a pulmonary artery pressure of 30/12 mm. Hg: while one patient in group B, although only 9 years of age, had a pulmonary index of but 4.8 liters and a pulmonary artery pressure of 83/56 mm. Hg. These two patients demonstrate the apparent lack of relationship between duration of flow as reflected in the age of the patient, magnitude of the flow, and the development of pulmonary hypertension.

The patients in the normotensive group revealed evidence of large left to right blood flows, with the oxygen saturation of the pulmonary artery blood samples averaging 85.5 per cent, and the mean pulmonary index being 13.2 liters. Patients comprising the hypertensive group, however, revealed considerable variation in the pulmonary artery blood oxygen saturation, with levels ranging from as low as 23 per cent to a high of 89.4 per cent. The mean saturation level was, therefore, considerably less than that of the normotensive group, being 70.9 per cent.

There was likewise considerable variation in the magnitude of the pulmonary blood flow in group B; the pulmonary index varied from 1.4 to 18.7 liters. The patient with the markedly lowered pulmonary artery blood oxygen saturation of 23 per cent and the lowest pulmonary index of 1.4 liters revealed the most severe

pulmonary artery hypertension with a level of 153/76 mm. Hg. This 30 year old patient had been cyanotic for several years and presented in right heart failure. Necropsy examination a few weeks following catheterization demonstrated a large atrial septal defect as the sole anomaly. There was also present marked dilation of the right atrium, and great dilation and hypertrophy of the right ventricle, together with widespread pulmonary occlusive disease.

The total pulmonary artery resistance was low in the patients in group A, the mean being 122 dynes, second, cm.$^{-5}$. The patients in the hypertensive group revealed an elevated total pulmonary artery resistance, the mean being 770 dynes, second, cm.$^{-5}$.

Case Reports of Five Patients with Closure of an Atrial Defect

Case 1, C. C., a 6 year old white girl, was found to have a cardiac murmur shortly after birth. Growth and development were normal, and there was no limitation of the exercise tolerance at any time. From the age of 4 to 6 years there was an increased frequency of upper respiratory infections.

Physical examination revealed slight asymmetry of the thorax with prominence of the precordium. The heart was not enlarged and no thrills or shocks were palpable. The second heart sound in the second left intercostal space was widely reduplicated but was normal in intensity. A grade II systolic murmur, rough and blowing in quality, was audible along the left sternal border with maximum intensity in the second left intercostal space.

The electrocardiogram demonstrated an rsR′ type of QRS complex in lead V_1 with a delayed intrinsicoid deflection time. The tracing was interpreted as indicating incomplete right bundle branch block.

Fluoroscopic examination revealed a considerable increase in the vascularity of the lung fields. The main pulmonary artery and the right and left main branches were increased in size and showed an increased amplitude of pulsations. The right atrium and right ventricle were enlarged.

Cardiac catheterization studies (table 2) revealed a rise in the blood oxygen saturation at the right atrial level indicating a left-to-right shunt. There was a considerable increase in the pulmonary blood flow and a slight increase in the right ventricular pressure.

Surgical correction of the defect was performed on May 25, 1953. Ventricular fibrillation occurred during the period of reduction of body temperature and prior to the opening of the chest. The thorax was immediately opened and cardiac massage instituted. A short period of cardiac standstill next occurred, followed by an idioventricular rhythm. The venae cavae were occluded, the right atrium opened and a large atrial septal defect closed with interrupted sutures. The postoperative course was complicated by the occurrence of atelectasis in the right lower lobe. The patient was discharged on June 8, 1953.

Three months postoperatively the patient was asymptomatic. Examination revealed a persistence of the reduplication of the second heart sound in the second left intercostal space. The systolic murmur along the left sternal border was decreased in intensity. There was no significant change in the electrocardiogram. Fluoroscopic examination showed no change in the vascularity of the lung fields or size of the pulmonary arteries. There was, however, a definite decrease in the amplitude of pulsations in the pulmonary arteries. There was also slight decrease in the size of the right atrium and right ventricle, so that the over-all heart size was within normal limits.

Postoperative cardiac catheterization was performed on Aug. 26, 1953. There was a normal oxygen saturation in the pulmonary artery with no evidence of a left-to-right shunt at the atrial level. The pulmonary artery and right ventricular pressures were slightly decreased (table 2).

Case 2, A. C., a 6 year old white boy, was one of nonidentical twin boys delivered without difficulty following a normal pregnancy. A cardiac murmur was detected at birth and has been present since. Frequent respiratory infections and slow weight gain occurred during the first two years of life. Since the age of 2 years the patient has been asymptomatic.

The physical examination revealed an active precordium with an apical thrust. A grade III blowing, systolic murmur was present along the left sternal border with maximum intensity in the second left intercostal space. The second heart sound in the second left intercostal space was increased in intensity and widely reduplicated. A medium pitched, soft, mid-diastolic murmur of short duration was audible along the lower left sternal border with transmission toward the apex (fig. 1).

The electrocardiogram demonstrated an incomplete right bundle branch block pattern. The fluoroscopic examination revealed an increased vascularity of the lung fields. The main pulmonary artery and the left and right pulmonary arteries were increased in size and amplitude of pulsations. The aorta was inconspicious in all views. The right atrium and right ventricle were slightly enlarged.

Cardiac catheterization revealed a rise in blood oxygen content at the right atrial level indicating a left-to-right shunt (table 2) with a pulmonary blood flow of considerable magnitude. The right ventricular pressure was slightly elevated, whereas the pulmonary artery pressure was normal, resulting in a pattern of functional pulmonic stenosis (fig. 2).

Surgical closure of the atrial defect was accom-

TABLE 2.—*Catheterization Studies in Five Patients before and after Closure of an Atrial Septal Defect.*

Name, Age and Sex	Time of Studies	Pressures, mm. Hg								Total Pulm. Artery Resistance Dynes/sec./cm.$^{-5}$	Pulm. Arteriolar Resistance Dynes/sec./cm.$^{-5}$	Oxygen Content, Per Cent Saturation								Cardiac Output		Cardiac Index	
		Right Atrium Mean	Right Ventricle Syst./Diast.	Pulm. Art. Syst./Diast.	Pulm. Art. Mean	Pulmonary "Capillary" Mean	Brachial or Femoral Art. Mean	Left Ventricle Syst./Diast.	Left Atrium Mean			Superior Vena Cava (S.V.C.)	Inferior Vena Cava (I.V.C.)	$\frac{\text{S.V.C.} + 2\,\text{I.V.C.}}{3}$	Right Atrium	Right Ventricle	Pulm. Artery	Left Atrium	Left Ventricle	Brachial or Femoral Artery	System. cc./min.	Pulm. cc./min.	System. L/min./M^2	Pulm. L/min./M^2
1. C.C. Age 6, female	Preop.	6	32/4	27/16	20	—	88/71	—	—	198	—	113.7 67.7%	120.5 71.8%	118.2 70.4%	134.0 79.7%	137.0 87.6%	140.6 83.7%	—	—	149.0 88.7%	2210	8095	3.6	13.2
	Postop. 3 mos.	1	25/−2	20/10	13	5	120/90	—	—	221	136	121.4 73.5%	127.5 77.2%	125.5 75.9%	122.0 73.8%	128.9 78.1%	128.5 78.0%	—	—	157.9 95.6%	4700	4700	6.1	6.1
2. A.C. Age 6, male	Preop.	1	39/−3	20/4	9	4	86/65	—	—	24	13	108.1 65.5%	127.1 77.0%	120.7 73.16%	148.1 83.8%	144.8 87.5%	147.7 89.5%	—	—	153.2 92.8%	5090	30,000	6.8	40.0
	Postop. 3 mos.	2	28/1	29/13	18	6	100/65	—	—	361	240	117.6 71.7%	103.3 63%	108.3 67.83%	106.4 64.90%	109.0 66.55%	107.4 66.50%	—	—	145.5 88.8%	3990	3990	4.7	4.7
3. J.G. 4 mos., female	Preop.	—	26/4	18		—	—	101/11	—	328	—	84.1 52.8%	70.5 44.3%	75.0 47.1%	129.0 63.75%	—	—	151.4 95.2%	152.8 96.0%	—	1285	4375	2.9	9.7
	Postop. 7 days	5	15/3	15/7	10	—	92/37	—	—	304	—	63.0 46.5%	75.6 55.8%	71.4 51.8%	66.0 48.7%	71.2 53.4%	78.9 58.2%	—	—	116.2 91.1%	2630	2630	5.3	5.3
4. G.H. Age 26, female	Preop.	7 (11/5)	100/1	100/30	53	12	113/84	122/−2	5 (14/5)	329	253	104.0 54.9%	124.8 65.9%	118.0 62.2%	161.3 85.1%	164.1 86.5%	163.8 86.4%	177.1 93.4%	—	179.5 94.7%	3300	12,900	2.9	8.9
	Postop. 4 mos.	1	30/0	30/17	21	—	104/63	—	—	364	208	104.0 59.1%	—	—	122.3 69.5%	124.8 71.0%	124.6 69.8%	—	—	168.9 96.0%	4600	4600	3.0	3.0
5. E.M. Age 19, female	Preop.	1	56/0	56/12	27	6	—	—	—	184	157	121.0 70.0%	—	—	149.0 86.1%	145.0 83.8%	140.0 81.0%	—	—	165.0 95.4%	5300	11,600	3.27	7.0
	Postop.	−1	25/−6	24/3	10	—	—	—	—	181	—	106.0 62.0%	124.0 72.4%	118.0 69.0%	116.0 67.8%	118.0 69.0%	116.0 67.8%	—	—	163.0 95.0%	4410	4410	2.85	2.85

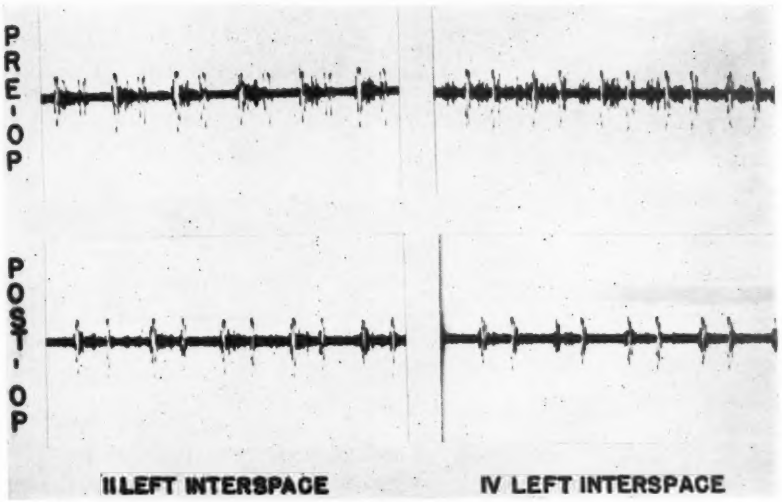

FIG. 1. Case 2, A. C. The phonocardiograms on the left were obtained in the second left intercostal space. A decrease in the intensity of the systolic murmur may be noted postoperatively. The phonocardiograms in the right hand column were obtained in the fourth left intercostal space, 2 cm. to the left of the sternal border. It may be noted that there is a disappearance postoperatively of the mid-diastolic murmur.

plished on June 26, 1953. The postoperative course was uneventful.

Examination three months postoperatively revealed no cardiac murmurs. The second heart sound in the left second intercostal space continued to be increased in intensity and reduplicated. There was no significant change in the electrocardiogram. Fluoroscopic examination revealed a decrease in the heart size. There was continued enlargement of the pulmonary arteries; however, the amplitude of pulsations of these vessels had decreased to normal. Recatheterization (table 2) revealed no evidence of a left-to-right shunt at the atrial level and normal pressures in the right ventricle and pulmonary arteries (fig. 2).

Case 3, J. G., a 4 year old girl, was known to have a cardiac murmur from the age of 3 months. The child developed normally and has been asymptomatic.

Physical examination revealed a normal heart size and no palpable thrills or shocks. The second heart sound in the second left intercostal space was increased in intensity and was widely reduplicated. A grade III blowing systolic murmur was audible along the left sternal border with maximum intensity in the second left intercostal space. A short medium pitched mid-diastolic murmur was audible along the lower left sternal border with transmission to the apex.

The electrocardiogram revealed a pattern of right ventricular hypertrophy. Fluoroscopic examination demonstrated increased vascularity of the lung fields. The main pulmonary artery and the right and left pulmonary arteries were increased in size and showed an increased amplitude of pulsations. The right atrium and right ventricle were enlarged.

Cardiac catheterization was performed on July 21, 1953, and revealed (table 2) a left-to-right shunt at the atrial level.

A thoracotomy was performed on Dec. 1, 1953 under hypothermia. The atrial septal defect was closed under direct vision with the aid of occlusion of the circulation for five minutes.

The postoperative course was uneventful. Results of postoperative cardiac catheterization on Dec. 8, 1953, showed no left-to-right shunt at the atrial level. Physical examination revealed that the previously described systolic and diastolic murmurs were no longer present. Fluroscopy demonstrated a decrease in the heart size to within normal limits. There was a persistence of the enlargement of the pulmonary arteries but normal pulsations were present in these vessels. There was no significant change in the electrocardiogram.

Case 4, G. H., a 26 year old, white woman, had noted limitation of exercise tolerance since childhood. A cardiac murmur was first detected when the patient was 5 years old. A progressive decrease in exercise tolerance with severe dyspnea had occurred so that by the time of the preoperative examination walking tolerance was limited to one block.

The physical examination revealed enlargement

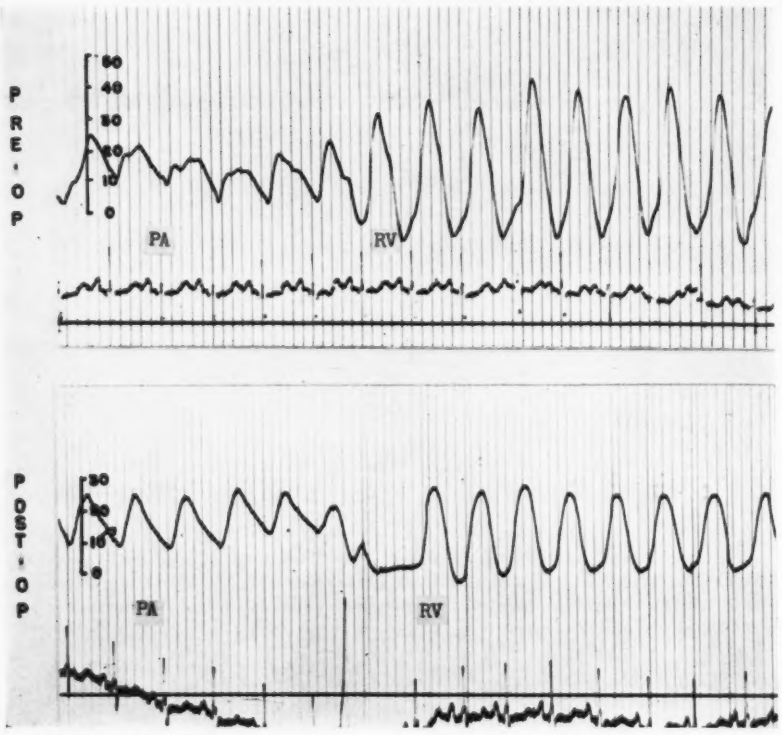

FIG. 2. Case 2, A. C. Pressure recordings during withdrawal of catheter from pulmonary artery (PA) into right ventricle (RV). The preoperative tracing shows a pressure rise at the ventricular level representing functional pulmonic stenosis. This pressure gradient is no longer present in the postoperative tracing.

of the heart to the left. A systolic thrust followed by a shock was palpable in the second left intercostal space. A tapping impulse was palpable along the lower left sternal border. The second heart sound in the second left intercostal space was slightly reduplicated. A grade III rough systolic murmur was audible along the left sternal border with maximum intensity in the third intercostal space.

The electrocardiogram demonstrated a pattern of right ventricular hypertrophy and partial right bundle-branch block. The fluoroscopic examination revealed an increased vascularity of the lung fields. The main pulmonary artery and the right and left main branches were considerably dilated and showed an increased amplitude of pulsations. The over-all heart size was increased with marked enlargement of the right atrium and right ventricle.

Cardiac catheterization was performed on April 14, 1953, and demonstrated a marked pulmonary artery pressure elevation and the presence of an atrial septal defect (table 2) with a left-to-right shunt at this level.

Direct surgical closure of a large atrial defect was accomplished on April 15, 1953, with hypothermia and cardiac inflow stasis. The postoperative course was complicated by the occurrence of supraventricular arrhythmias.

A considerable increase in the patient's exercise tolerance occurred postoperatively. Four months following surgery the patient was able to walk half a mile.

Physical examination revealed a decrease in the intensity of the second heart sound in the second left intercostal space and a decrease in the intensity of the systolic murmur from grade III to grade I. There was a definite decrease in the heart size by roentgenologic examination (fig. 3). There was a decrease in the vascularity of the peripheral lung fields and a considerable decrease in the amplitude of pulsations over the main pulmonary artery and the right and left main branches.

The electrocardiographic studies postoperatively showed a decrease in the amplitude of the R wave in lead V_1 and a decrease in the depth of the S wave in lead V_6. Postoperative physiologic studies demonstrated a dramatic decrease in the previously el-

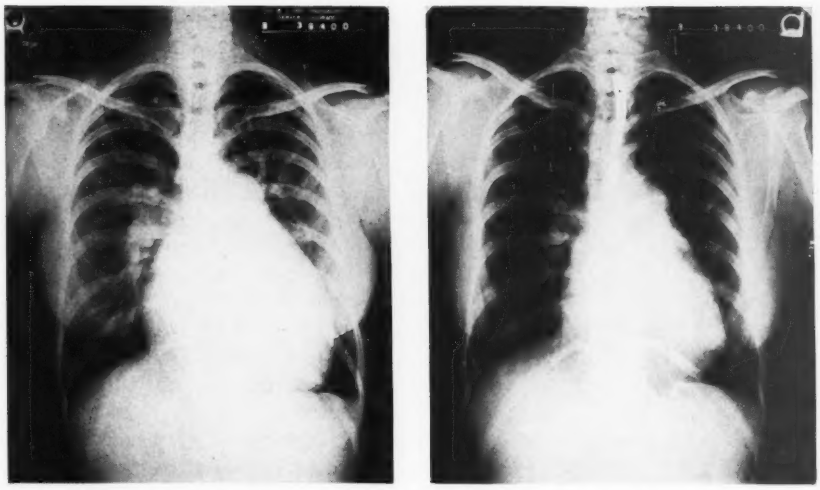

FIG. 3. Case 4, G. H. The chest roentgenogram preoperatively (*A*) and four months postoperatively (*B*).

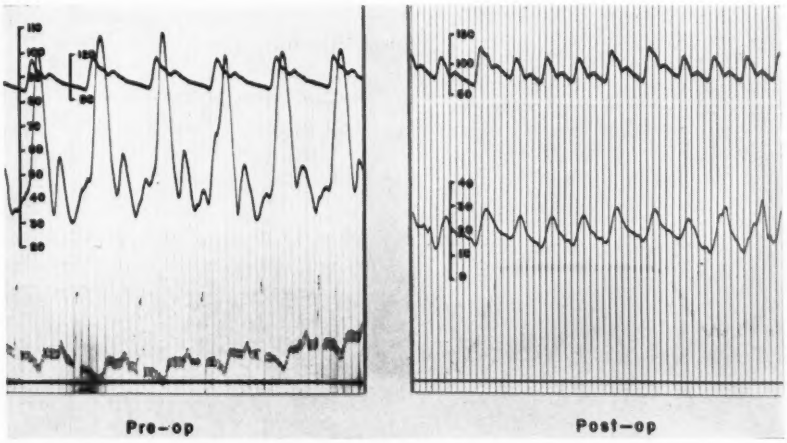

FIG. 4. Case 4, G. H. The preoperative pulmonary artery pressure contour is shown on the left in the lower of the two pressure tracings. A marked elevation to average levels of 100/30 mm. Hg is noted. The postoperative pulmonary artery pressure on the right shows a marked decrease in pulmonary artery pressure to average levels of 30/15 mm. Hg. The upper pressure tracing in both panels represents the brachial artery pressure.

vated pulmonary artery pressure (fig. 4) and showed no evidence of a left-to-right shunt at the atrial level.

Case 5, M. E., a 19 year old white woman, was thin and easily fatigued during childhood. Respiratory infections occurred frequently during childhood and adolescence, with episodes of pneumonia. A diagnosis of heart disease was made at age 10 years, when a murmur was first detected. Preoperatively the patient complained of dyspnea and ease of fatigue.

Physical examination revealed asymmetry of the thorax with prominence of the precordium. Palpation demonstrated an overly active precordium with a thrust in the epigastrium and along the lower left sternal border. A shock was palpable in the second left intercostal space. Auscultation revealed an accentuated, widely reduplicated second heart sound in the second left intercostal space. A grade III rough blowing systolic murmur was present along the left sternal border with maximum intensity in the

third left intercostal space. A low-pitched, short, mid-diastolic murmur was audible between the lower left sternal border and the midclavicular line.

The electrocardiogram revealed a pattern of right bundle-branch block and right ventricular hypertrophy.

Fluoroscopy showed an increased vascularity of the lung fields. The main and right and left pulmonary arteries were greatly increased in size and showed an increased amplitude of pulsations. The right atrium and right ventricle were considerably enlarged.

Cardiac catheterization data demonstrated a moderately severe pulmonary hypertension (table 2) and an increased pulmonary blood flow with a left-to-right shunt at the atrial level.

On Aug. 28, 1953, a large atrial septal defect was closed under direct vision with the aid of hypothermia and inflow and outflow stasis.

The postoperative course was complicated by recurring episodes of chest pain and fever. Cardiac catheterization studies postoperatively on Oct. 15, 1953, showed a normal pulmonary artery pressure and no evidence of a left-to-right shunt at the atrial level. Three months after surgery the patient was asymptomatic, performing all household activities, and had walked one mile without fatigue. Physical examination revealed that the previously described systolic and diastolic murmurs were no longer present. The intensity of the second heart sound in the second left intercostal space was reduced, but continued to be reduplicated. There was a decrease in the size of the right atrium and right ventricle by fluoroscopic examination. There were no significant alterations in the electrocardiogram.

Discussion

Selection of Patients for Closure

Now that it has been established that atrial septal defects can be successfully closed, the problem of the selection of candidates for the procedure arises. The great variability in the natural history of patients with this defect has long been recognized. Thus at this stage in the development of the operative procedure, it would be of great value could one differentiate those patients who will enjoy relative longevity from those who will develop pulmonary artery hypertension leading to serious disability and possibly death early in their lives.

However, a review of the studies of our patients with atrial septal defects reveals that such a prediction is difficult, if not impossible, to accomplish. An evaluation of this group of 25 patients does not suggest that age in itself is a significant factor in the development of pulmonary hypertension. Thus, it is noted that there is no significant difference between the average ages in the two groups that were formed on the basis of the level of their pulmonary artery pressure. Also, it may be noted that the extremes of age in the two groups show no great difference.

The patients with normal pulmonary artery pressure had pulmonary artery blood flows of the greater magnitude. Thus, it would appear that neither the duration nor the magnitude of the pulmonary artery blood flow in themselves are of critical significance in the development of pulmonary artery hypertension. There are factors other than age and magnitude of pulmonary blood flow to be considered in the development of pulmonary hypertension in patients with atrial septal defects. An evaluation of these factors is beyond the scope of this paper.

The total pulmonary artery resistance was within normal limits in the patients with normal pulmonary artery blood pressure despite the presence of greatly increased pulmonary artery blood flows. This reflects the capaciousness and great distensibility of the normal pulmonary vascular bed. The group of patients with pulmonary artery hypertension, however, revealed a considerable increase in the total pulmonary artery resistance. The development of pulmonary artery hypertension with the resulting decrease in the magnitude of the pulmonary blood flow, suggests a loss of the normal distensibility of the pulmonary vascular bed and the development of occlusive changes in the smaller pulmonary arteries and arterioles. Currently there would not appear to be any recognized factor that portends the development of pulmonary hypertension in patients with atrial septal defects.

At the present time closure of atrial septal defects under direct vision is being advised in patients having a pulmonary blood flow three times the value of the systemic flow. This is purely an arbitrary level and will doubtlessly be altered as experience dictates. The presence of pulmonary hypertension does

not in itself negate the possibility of successful operative therapy. Patient G. H. is an excellent example of the dramatic benefits, both physiologic and clinical, that may result from closure of an atrial septal defect even in the presence of marked pulmonary hypertension. However, the presence of pulmonary hypertension does call for careful evaluation of the patient. When there is moderate to marked pulmonary artery hypertension with a high diastolic pressure level, associated with a normal or slightly elevated pulmonary artery blood flow then it is considered inadvisable to recommend surgical closure of the defect.

It is anticipated that with increasing experience the present criteria will be altered and the indication for surgical therapy in patients with an atrial septal defect will be the diagnosis of the uncomplicated anomaly.

Operative Technic of Closure

Experience in this institution with several types of indirect techniques for the closure of atrial defects led to the realization that, despite good results in the experimental laboratory, indirect methods did not secure complete closure of the large defects frequently encountered clinically. Accordingly, we have recently turned to the method first described by Lewis and Taufic[10] of closure under direct vision with the aid of hypothermia and cardiac inflow occlusion. The technical aspects of this procedure have recently been reported by Swan and associates.[11]

Briefly, the body temperature is lowered to approximately 30 C. by placing the anesthetized patient in a tub of ice water. The patient is then removed to the operating room with a continued fall in body temperature to the neighborhood of 24 C. An anterior transverse sternum splitting bilateral thoracotomy is then performed. At this temperature it is considered safe to totally occlude circulation for periods up to 10 minutes. The right atrium is then opened and the septal defect closed under direct vision with interrupted silk sutures. It is of the utmost importance that measures be taken to prevent coronary air embolism at the time of closure of the right atrium.

Hemodynamic Changes Following Closure

The striking feature of the postoperative catheterization data (table 2) is the evidence of complete closure of the atrial septal defect in all patients. The mixed venous blood samples as obtained from the venae cavae and right heart chambers revealed no significant rise at any level. Moreover, the oxygen content of the blood samples at the pulmonary arterial level was within normal limits. An inferior vena caval sample was not obtained in patient G. H. during the postoperative catheterization, thus making it impossible to accurately evaluate the significance of the oxygen content at the atrial level. The fact that the oxygen saturation of the pulmonary artery blood sample was normal compared with the elevated preoperative level indicates the absence of a left-to-right shunt.

An equally striking change was the decrease in pulmonary artery blood pressure noted postoperatively in the two patients with significant pulmonary artery hypertension. In patient G. H. the preoperative pulmonary artery pressure was 100/30, whereas the pressure four months postoperative was 30/17 (fig. 4). A significant decrease in the pulmonary artery pressure occurred postoperatively in patients J. G. and C. C. although the preoperative pulmonary artery pressures were within normal limits. This decrease in the pulmonary artery pressures indicates the presence of a normal pulmonary vasculature and suggests that the slight preoperative elevations were a result of a disproportion between the greatly elevated pulmonary blood flow and the capacity of a normal pulmonary vascular bed. The persistance of slight pulmonary artery hypertension postoperatively in patient, G. H., suggests the possibility of structural changes in the pulmonary vascular bed.

The preoperative pressure gradient recorded between the right ventricle and pulmonary artery in patient A. C. represents functional pulmonic stenosis. This phenomenon reflects a greatly elevated pulmonary artery blood flow, and does not indicate anatomic stenosis of the pulmonary valve. This interpretation of the pressures is clearly substantiated by the

postoperative pressure tracing demonstrating complete disappearance of the gradient (fig. 2). This phenomenon of functional pulmonic stenosis should be considered when entertaining a diagnosis of mild, pure pulmonic stenosis.

The total pulmonary artery resistance was moderately elevated postoperatively in three patients. This finding again suggests residual structural changes at the level of the small pulmonary arteries and arterioles.

Preoperatively the systemic blood flow was considered to be within normal limits in all five cases. This has been the usual finding in our patients with atrial septal defects, and it is not thought that these patients have decreased systemic blood flows. Postoperatively no consistent change in the systemic blood flow was observed. Preoperatively the pulmonary blood flow was significantly increased in all patients, ranging from a calculated pulmonary index of 7 liters to 40 liters. Postoperatively there was a marked reduction in the pulmonary artery blood flow to levels equalling the systemic blood flow.

The physiologic data obtained postoperatively in these five patients reveals complete closure of the atrial septal defect in all patients. The hemodynamic picture has returned to normal with the exception in some instances of possible residual structural changes in the smaller pulmonary arteries and arterioles.

Clinical Changes Following Closure

Dyspnea and ease of fatigue were prominent features of the preoperative course in patients G. H. and M. E. Postoperatively, there was great amelioration of these symptoms. The mechanisms resulting in dyspnea in patients with atrial defects are not well established. The resting systemic blood flow and the peripheral arterial oxygen saturation were within normal ranges in these patients, thus tending to minimize the role of systemic hypoxia as a significant factor in the genesis of these symptoms. A more important mechanism may be the decrease in resiliency and elasticity of the lungs of patients with large pulmonary blood flows due to the engorgement of the pulmonary vasculature. Dyspnea may thus result from the increased respiratory effort necessitated in the presence of these "stiffened" lungs, and by the continued stimulation of the Hering-Breuer reflex.

The changes in the cardiac murmurs noted postoperatively are of interest in evaluating their origin. The systolic murmur present in all patients over the pulmonic area had disappeared in two patients and had greatly diminished in intensity in the remaining three patients (fig. 1). This would tend to substantiate the opinion that this murmur arises as the result of the increased blood flow through the pulmonary artery, and is in effect the murmur of functional pulmonic stenosis. The persistence of the murmur postoperatively in three patients in all probability reflects the continued presence of turbulent blood flow in the dilated pulmonary artery and establishes the fact that this murmur is not a result of flow through the atrial septal defect itself.

The preoperative examination in three patients revealed a medium-pitched, short, mid-diastolic murmur along the lower left sternal border. This murmur disappeared postoperatively in all three patients (fig. 1). The disappearance of this murmur postoperatively strongly suggests absence of associated mitral stenosis. Palpation of a normal mitral valve orifice at surgery offers incontestible evidence of the presence of a normal mitral valve. It is emphasized, therefore, that the presence of this diastolic murmur in a patient with an atrial septal defect does not necessarily indicate the association of anatomical mitral valve stenosis. This combination of mitral stenosis and an atrial septal defect, termed Lutembacher's syndrome, is an established entity. However, the present findings emphasize the fact that this lesion is diagnosed on a clinical basis much more frequently than is justified by its rare occurrence. The basis for the murmur in question is considered to be the greatly increased blood flow through the tricuspid valve, thus representing a functional tricuspid stenosis. In support of this explanation is the location of the murmur along the lower left sternal border in contrast to the apical location of the diastolic murmur heard frequently in patients with a patent ductus arteriosus or a large ventricular septal defect in which case

the murmur results from a functional stenosis of the mitral valve.

Reduplication of the second heart sound in the second left intercostal space persisted postoperatively. The physiologic basis for this finding has not been well established. It is significant in this regard that there was also persistance of incomplete right bundle branch block electrocardiographically. The intensity of the second heart sound was significantly decreased in the two patients who had presented evidence of pulmonary hypertension preoperatively.

Minor changes were noted on comparing the pre- and postoperative electrocardiograms in these five patients. A decrease in the amplitude of the R′ wave in lead V_1 and a decrease in the depth of the S wave in lead V_6 occurred in patients A. C. and G. H., suggesting a decrease in the element of right ventricular hypertrophy. There was a persistence of the partial right bundle-branch block pattern in the four patients revealing this finding preoperatively. The subsequent outcome of the conduction defect in these patients may be helpful in determining the origin of this electrocardiographic abnormality.

The postoperative roentgenographic studies showed a decrease in heart size in all instances. This decrease was most prominent in the two patients who preoperatively showed the greatest increase in heart size and revealed definite evidence of pulmonary hypertension. The early postoperative decrease in heart size may be a reflection of the decrease in the total blood volume which occurs following closure of the atrial septal defect. Further decrease in heart size may be a reflection of the diminished work load of the right heart and may indicate an actual decrease in the size of the right ventricle and right atrium. In contrast to the decrease in the size of the right heart chambers the pulmonary artery remained dilated postoperatively in all patients. There was, however, a decrease to within normal limits of the previously increased amplitude of pulsation in these vessels.

Thus there has been definite evidence of the abolishment or improvement in all signs and symptoms that preoperatively were related to the great increase in the pulmonary artery blood flow.

Summary and Conclusions

1. Five patients are presented in whom an atrial septal defect was closed under direct vision under conditions of open heart surgery.

2. Clinical and hemodynamic studies obtained postoperatively are compared with the preoperative findings and their significance discussed.

3. Evaluation of physiologic data did not reveal significant criteria portending the development of pulmonary hypertension in patients with an atrial septal defect.

4. Indications for surgical closure in a patient with an atrial septal defect are presented.

Acknowledgment

The authors are indebted to Colonel Edwin M. Goyette, chief of Cardiology, Fitzsimons Army Hospital for permission to include case 5, E. M., in this study.

Sumario Español

1. Cinco pacientes se informan en los cuales un defecto del septo atrial se cerró bajo observación directa en condiciones de cirugía cardíaca abierta.

2. Los estudios clínicos y hemodinámicos postoperatorios obtenidos se comparan con los hallazgos preoperatorios y el significado se discute.

3. Evaluación de los datos fisiológicos no reveló criterios significativos presagiando el desarrollo de hipertensión pulmonar en pacientes con defecto del septo atrial.

4. Las indicaciones para el cierre quirúrgico de defecto del septo atrial se presentan.

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The Circulation in Cold Acclimatization

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The hand and forearm blood flow of the Eskimo has been found to be greater than that of a control group of white persons in a temperate climate both at rest at an ambient temperature of 20 C. and during acute cold exposure. Under cold stress, rectal temperature was better maintained in the Eskimos, though certain deep muscle temperatures fell more than they did in the white men because of the greater blood flow through exposed parts. The Eskimos showed an elevation of basal metabolic rate and of plasma and total red cell volume. There are similarities between the circulatory changes found in the Eskimo and those found in hyperthyroidism.

IT IS well known that the effects of acute cold exposure are peripheral vasoconstriction, diuresis and hemoconcentration. Two questions arise in connection with long-term cold exposure or cold acclimatization. Is the vascular response to acute cold exposure different in the acclimatized person? Does the acclimatized person, as compared with the unacclimatized, show changes in peripheral circulation when both are at a reasonably comfortable ambient temperature? Studies of the vascular dynamics of acclimatized persons have so far been few. The most important have been those of Balke, Cremer, Kramer and Reichel[1] who studied skin temperature changes in men exposed to moderate cold for 28 days, and those of Carlson and his colleagues[2, 3] who studied skin, muscle and rectal temperatures in subjects who had been exposed for various times. In this report there are presented the results of studies of peripheral blood flow, skin, subcutaneous, muscle and rectal temperatures in acclimatized and non-acclimatized subjects, both during acute cold exposure and at a comfortable ambient temperature. Data have also been obtained on the basal metabolic rate and on the blood volume while at rest.

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Methods

The cold-acclimatized subjects for these experiments were chosen from Eskimos on Southampton Island, Northwest Territories. Here the Eskimo still live the traditional native life and gain their livelihood by hunting, fishing and trapping. They are thus frequently exposed to cold. The experiments on the Eskimos were performed during July and August 1949 and 1950, months during which they live in shacks or tents. The mean daily maximum temperature for July and August over a seven-year period (1943–1950) was 53.6 F., and the mean daily minimum temperature was 38.1 F. During January, when the Eskimos live in shacks or igloos, the mean daily maximum and minimum temperatures, over the same seven-year period, were −16.7 F. and −32.5 F., respectively. Temperatures recorded at 6:30 a.m. in two representative shacks during the month of April ranged between 28 F. and 52 F. In two igloos, at the same time of day and during the same month, temperatures between 17 F. and 32 F. were recorded.

Fifty-nine healthy male Eskimos between 18 and 50 years of age were used for the peripheral circulatory and tissue temperature studies. They were not all full-blooded Eskimos. Measurements of the blood flow in the hand and forearm were made with a Lewis-Grant type of venous occlusion plethysmograph. The temperatures of the skin, subcutaneous and muscle tissue of the forearm, skin of the hand, and rectal temperature were obtained with thermocouples. Skin temperature of the hand was recorded from the thenar eminence, the dorsum of the hand and the dorsal surface of the distal phalanx of the first, third and fifth fingers. The average value is reported. The blood pressure was recorded with a sphygmomanometer, and the heart rate was counted from the radial pulse. For all studies the subjects lay on a couch with trunk and head elevated to an angle of 30 degrees and arms at heart level. A 30-minute rest period was allowed before any measurements were made. Room temperature was kept at

20 C ± 0.5 C. and relative humidity at 50 to 60 percent.

Four groups of observations were made. (1) The temperatures of the forearm tissues were measured immediately after the forearm was bared, and these temperatures, recorded within one minute after baring, were considered the temperature of the clothed forearm. Rectal temperatures were recorded at the same time. (2) With the arms exposed to room air at 20 C., the temperature and blood flow in the artificially clothed forearm and the hand (cotton wool) were recorded over a two-hour period. The plethysmographs were not ventilated. (3) Hand blood flow, and temperature and blood flow in the forearm were measured during direct exposure of the hand and forearm to waterbaths at 5 C., to 45 C. Except for the experiments in the control group at 5 C., the observations were made over a two-hour period. (4) The hand blood flow and the forearm blood flow and temperature were measured over a two-hour period during which the feet and legs were cooled or heated by immersing both lower extremities in a water bath up to a point five inches below the upper end of the tibia. The cold bath was 10 C. and the hot was 42.5 C. In these experiments the forearm blood flow was measured at a water-bath temperature of 34 C. and the hand blood flow at 32 C., water-bath temperatures which had been found to maintain flows similar to those seen in the hand and clothed forearm at a room temperature of 20 C.

The control group used for the vascular experiments was composed of 85 male, healthy medical students, who were studied during September and October 1951, at which time the outdoor temperature in Kingston, Canada, corresponded to the outdoor temperature on Southampton Island during July and August. The clothing worn by the Eskimos and by the control group was the same (wool shirts, trousers, underwear, socks) except that the Eskimos wore sealskin mukluks and the medical students wore oxfords.

Basal metabolic rate was determined in four male and four female Eskimos between 18 and 45 years of age. Oxygen consumption was measured with a Benedict-Roth type of spirometer, DuBois charts were used to determine surface area, and DuBois' standards as modified by Boothby and Sandford were taken as the normal. Only those subjects were used from whom two satisfactory tracings were obtained during preliminary tests. All subjects were studied in the fasting state between 4:30 and 9 a.m., while they were still in bed in their own tents or shacks. Blood volume was determined by a modification of the method of Gregerson[4] in eight male Eskimos between 17 and 27 years of age.

Results

Peripheral Circulation

The Eskimos were found to be comfortable at a much lower ambient temperature than were the members of the control group, and it was after a survey of temperatures of their shacks and tents in July that 20 C. was finally

Table 1.—*Blood Flow and Tissue Temperatures at Room Temperature 20 C.*

	Group	No. of Subjects	Mean	S.E.M.	p
Forearm baring temperatures (C.)					
Skin	Control	33	30.5	±0.25	
	Eskimo	61	31.2	±0.17	0.02
Subcutan.	Control	33	32.7	±0.23	
	Eskimo	67	32.9	±0.18	0.49
Muscle	Control	30	34.4	±0.19	
	Eskimo	65	34.6	±0.16	0.41
Hand temp. (C.)	Control	5	32.6	±0.89	
	Eskimo	6	33.8	±0.47	0.21
Rectal temp. (C.)	Control	31	37.3	±0.07	
	Eskimo	30	37.1	±0.06	0.14
Forearm blood flow (cc./100 cc. tissue/min.)	Control	4	3.0	±0.08	
	Eskimo	6	5.2	±0.11	<0.01
Hand blood flow (cc./100 cc. tissue/min.)	Control	5	4.7	±0.19	
	Eskimo	6	8.6	±0.43	<0.01

selected as the ambient temperature at which the experiments would be carried out. At this temperature the average skin temperature of the clothed forearm of the Eskimos was higher than that of the white men ($p = 0.02$), though there was no difference in subcutaneous, muscle or rectal temperature (table 1). When the observations were continued for two hours with the hand or the arm in the plethysmograph, which provided rather more insulation for the part to be studied than did the cotton wool, it was found that the blood flows in both the hand and forearm were greater in the Eskimos. The higher bood flow in the Eskimos was accompanied by higher skin temperatures of both hand and forearm, and gradually rising subcutaneous and muscle temperatures. The rectal temperature was essentially the same in the two groups and remained unchanged.

When the limb being studied was immersed in a water bath at a slightly lower temperature (30 C.), there was little change in the volume of the hand blood flow but, as at all water-bath temperatures between 5 C. and 33 C., the blood flow was greater in the Eskimos (7.1 ± 0.43 as compared with 3.8 ± 0.23 cc. per 100 cc. of tissue per minute). The blood flow in the forearm was also greater (3.2 ± 0.12 as compared with 2.8 ± 0.16 cc. per 100 cc. of tissue per minute), though there was a

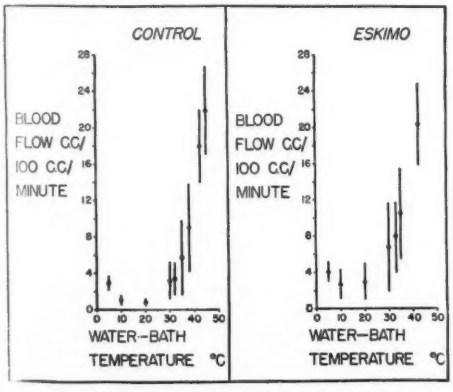

FIG. 1. Average hand blood flow at various water-bath temperatures. Each point is the average of the readings made every five minutes on three to five subjects (Eskimos at 35 C. and 42.5 C., only two subjects) during the last hour of exposure. The S.D. is indicated by the line.

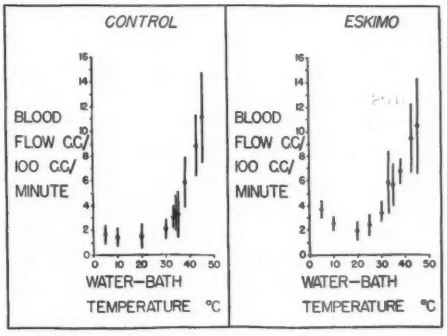

FIG. 2. Average forearm blood flow at various water-bath temperatures. Each point is the average of readings made every five minutes on three to six subjects (control group at 5 C. and Eskimos at 25 and 45 C., only two subjects) during the last hour of exposure. The S.D. is indicated by the line.

slow decrease in the volume of flow during the two-hour period (figs. 1 and 2). The subcutaneous temperature fell slightly and to the same degree in the two groups. Muscle temperature fell slightly more in the Eskimos than in the white men, and the rectal temperature remained unchanged.

When the limb was exposed for two hours to 10 C. and 20 C. water baths, there was a marked reduction in both hand and forearm blood flow and, in fact, it was at these temperatures that the lowest blood flows in hand and forearm were recorded (fig. 3). The rate of fall of the hand blood flow was always slower

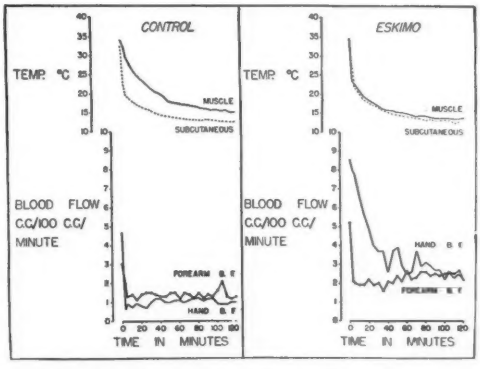

FIG. 3. Effect of immersion of hand and forearm in water-bath at 10 C. The results shown were obtained on groups of five in the hand studies and on four controls and five Eskimos in the forearm studies.

in the Eskimos than in the controls, but the rate of fall of the muscle temperature was faster in the Eskimos, though the final temperatures arrived at in both groups were not greatly different. The average rectal temperature fell 0.3 C. in both groups during the 20 C. experiment and 0.5 C. in the 10 C. experiment. With exposure of the hand and forearm to water at 20 C., there was no significant difference between the blood pressure changes seen in the two groups, but at 10 C. the average blood pressure of the Eskimo during the two-hour observation period (114/80) was significantly higher than in the previous rest period (101/63). The members of the control group, on the other hand, showed no change in blood pressure.

Exposure of the upper limb to extreme cold (5 C. water bath) was tolerated by the Eskimos without difficulty whereas the white men could stand it only for one hour. As with exposure to moderate cold, there was a difference in the blood pressure reactions. The average blood presure of the Eskimo during the two-hour period was 142/97 as compared with a resting level of 101/64. The white man showed a lesser elevation; 129/100 as compared with 123/91. On acute exposure of this type the hand blood flow was finally greater than at 10 C., and though the average flow was not as high in the white man as in the Eskimos, the increase in the blood flow over that seen at 10 C. was greater in the white man. In the forearm, the blood flow increased markedly in the Eskimo to approximate the levels recorded at water temperatures of 30 C. The control group showed very little increase in forearm blood flow. Though the forearm blood flow was more than twice as great in the Eskimo (3.8 ± 0.12 as compared with 1.5 ± 0.6 cc. per 100 cc. of tissue per minute), the muscle temperature at the end of an hour was 18 C. in the control group as compared with 12.5 C. in the Eskimo. Also, the rate of fall of muscle temperature was less in the control group. The behavior of the subcutaneous temperatures paralleled that of the muscle temperature. In the Eskimos, the rectal temperature after two hours was 0.5 C. below the preimmersion level; in the white men it was 0.7 C. lower after 50 minutes.

When the hand and forearm were exposed to heat as in a water bath at 42.5 C., subcutaneous and muscle temperature showed a marked increase and the final levels achieved were the same in the Eskimos as in the white men. The speed with which the high level was achieved was the same in the two groups. Both hand and forearm blood flows, however, were greater in the Eskimos, and in the case of the forearm, the rate at which blood flow increased was also greater in the Eskimos. Though the average final blood flow in forearm was less in the white man, the augmentation of blood flow which occurred on immersion in a warm bath was greater than that seen in the Eskimo, due to the fact that the initial levels were lower in the white man.

When heat was applied to the body by immersing the legs in water bath at 42.5 C.,

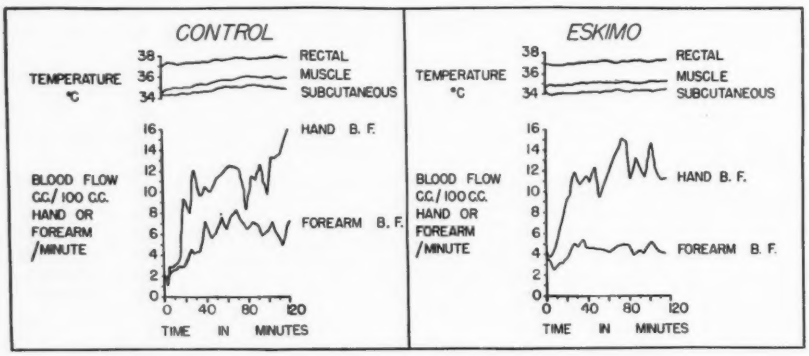

FIG. 4. Effect on hand and forearm blood flow and tissue temperatures of immersion of feet and legs in water bath at 42.5 C.

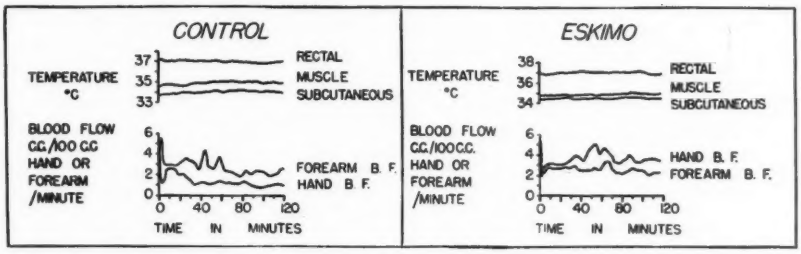

FIG. 5. Effect on hand and forearm blood flow and tissue temperatures of immersion of feet and legs in water bath at 10 C.

the blood flow of hand and forearm naturally increased (fig. 4). In the case of the hand, the final level of blood flow became the same in the two groups, which meant that the percentage increase was greater in the control group. In the forearm, the blood flow increased more rapidly in the control group and the final levels reached were higher. Forearm muscle temperature increased 1.5 C. in the white men as compared with 0.5 C. in the Eskimos. Subcutaneous tissue temperatures in both groups increased by 0.5 C. throughout the first hour, and the rectal temperature increased by 0.6 C. during the same period.

When heat was removed from the body by immersing the legs in a water bath at 10 C., the hand blood flow in the Eskimos fell slightly below the preimmersion level in 10 minutes and remained at approximately this level throughout the 2-hour period of the experiment (fig. 5). By contrast, the hand blood flow of the control group, after some variation for 15 minutes, fell to a much lower level, which was maintained throughout the two-hour period. The final result under these conditions was that the hand blood flow of the Eskimo was about twice that of the white man. In the same circumstances, there was no significant change in the forearm blood flow of the Eskimo, whereas after 30 minutes there was a fall in that of the white man. The alterations in blood flow were not accompanied by changes of any size in subcutaneous, muscle or rectal temperatures. In these experiments, as in all the others, the fluctuations from time to time in individual blood flows, in both the hand and the forearm, were greater in the Eskimos than in the white men.

Subjective Response to Cold

The ability of the Eskimo to withstand the cold was evident on casual observation. Swimming in the sea on the occasional fine day, pouring over themselves sea water at 2.0 C. on a cool September evening, and their ability to work with bare hands and to continue to perform fine movements in the winter cold are examples of this. At the same time, their heat tolerance is diminished, and they were often uncomfortable and perspiring while in our laboratory huts.

Differences from the white man were also noted in the sensations the Eskimo experienced after the application of local cold. When the arm was immersed in a water bath at 20 C. a transient sensation of coldness occurred in both groups. With the arm in the 10 C. water bath, the Eskimo experienced a sensation of coldness upon immersion but there was no pain, and the three subjects studied were asleep within 20 minutes. The four subjects in the control group experienced first a sensation of severe coldness in the immersed arm, and a deep, aching pain developed which reached maximum intensity in about three minutes and then decreased to disappear after about 10 minutes. The sensation of coldness persisted but diminished somewhat in intensity. None of the control group was able to sleep. When the arm was immersed in the 5 C. water bath, the Eskimo complained of severe coldness and also of a deep aching sensation during the first five minutes. Two of the three subjects were able to sleep within 20 to 30 minutes. The three men in the control group complained of severe local coldness upon immersion of the arm with the rapid development of a deep,

aching pain which reached its peak intensity within 1 or 2 minutes. In all the control subjects the sensation of coldness diminished but did not disappear, and throughout the entire period of immersion of the arm, transient burning sensations occurred in all three subjects. This sensation was restricted to the skin and was frequently precipitated or made worse by local pressure. None of these men was able to sleep.

Basal Metabolic Rate

Four series of determinations of the basal metabolic rate were made at approximately fortnightly intervals between July 11 and Aug. 29, 1949. The results as shown in table 2 indicate a significant elevation, which becomes less marked as the summer progresses.

TABLE 2.—*Basal Metabolic Rate of Eskimo in July and August*

	July 13–17	July 29–Aug. 2	Aug. 15–19	Aug. 25–29
Average B.M.R., %	29.3	25.8	22.3	21.8
S.D.	13.8	10.0	7.9	7.7

Blood Volume

The average blood volume of the Eskimos was found to be markedly elevated throughout the period of observation from July 12 to Aug. 20, 1950 (table 3). As with the basal metabolic rate, the elevation was greater in the earlier observations. An increase of both plasma and total red cell volume contributed to the increase in total blood volume, and the fall in plasma volume which occurred during the summer was greater than the fall in total red cell volume.

TABLE 3.—*Blood Volume in Eight Male Eskimos*

	Series 1 July 17–20		Series 2 Aug. 2–5		Series 3 Aug. 16–20	
	Av.	S.D.	Av.	S.D.	Av.	S.D.
Hematocrit, %	44.6	2.2	44.0	2.5	44.7	1.6
Plasma volume, cc./M.²	2424.1	337.1	2345.6	189.1	2236.9	227.2
RBC volume, cc./M.²	1941.4	298.1	1871.8	260.0	1818.4	240.0
Blood volume, cc./M.²	4365.5	595.9	4217.3	436.0	4055.3	453.3

Discussion

Consideration of these results and of reports of other experiments in the literature leads to the conclusion that the circulatory changes which follow exposure to the cold pursue a phasic pattern. On acute cold exposure it is well known that there is vasoconstriction, and accompanying this there is reduction of circulating blood volume.[5, 6, 7] If cold exposure is continued, there is some lessening of the vasoconstriction as shown by skin temperature changes.[8, 9] There is also a return of the circulating blood volume towards normal. This is hinted at by Bazett, Sunderman, Doupe and Scott,[5] and documented with experimental data by Spealman, Newton and Post.[7] Further continuation of cold exposure, or what can be termed long-term exposure, leads to complex changes. There is then subjective comfort at a lower ambient temperature[10] and, as reported now, a change in the pattern of the different types of discomfort which occur on severe local cold exposure. These subjective phenomena are accompanied by evidence of an enhanced peripheral circulation which persists between cold exposures. At a comfortable ambient temperature there is an increased blood flow through hand and forearm as compared with controls, and an increased skin temperature over hand and forearm,[10, 11, 12, 13] though only the difference in forearm skin temperature has been found to be statistically significant. This increase in peripheral blood flow at rest is accompanied by an increase in both plasma volume and total red cell volume which indicates that enhancement of the peripheral circulation is not necessarily accomplished at the expense of the visceral blood supply. It is the fact that the peripheral circulation and the blood volume behave in this phasic fashion in response to cold which has led to so much confusion in the literature concerning the effect of cold and the existence of acclimatization to cold in man. Actually, the findings in any particular experiment will depend on the previous cold experience of the subjects, the clothing, and the duration and severity of the cold

exposure, all of which should be defined in acute or short-term experiments.

In those who have been subjected to long-term cold exposure, that is, in those who may be said to be acclimatized, there are alterations in the response to acute cold which are rather complex. As in the unacclimatized, there is peripheral vasoconstriction. Comparative studies of cold diuresis and reduction in blood volume have not yet been made. In our experiments the reduction which was seen in the hand blood flow of the acclimatized Eskimo when the hand and forearm were placed in the 5 C. water bath, was actually greater than that recorded in the controls, but the final level at which blood flow stabilized at this temperature was higher than in the controls. In all water bath temperatures from 5 C. to 33 C. this enhanced blood flow has been seen in both hand and forearm in the Eskimos. The greater circulation of blood through the hand and forearm exposed to the cold means a greater cooling of the deep tissues of the forearm. A comparison of the tissue temperatures and the blood flows in these experiments with the tissue temperatures in our experiments in which the legs and feet were cooled, indicates that the lower muscle temperature in the Eskimo on severe cold exposure is due to cooling by the mechanism described by Pennes[14] and by Bazett, Love, Newton, Eisenberg, Day and Forster[15] and by Bazett, Mendelson, Love and Libet.[16] Carlson and his colleagues[2, 3] have also recorded muscle temperatures in the arm and leg which are consistent with this view.

The improved maintenance of rectal temperature in the acclimatized despite greater heat loss from the extremities, which has now been reported, could be the result of (1) greater cooling of other tissues than those in the body core and in the extremities, (2) more efficient control of heat loss from sites other than the extremities, or (3) greater heat production during the period of exposure. Attention has been drawn by Carlson and his colleagues[2, 3, 12] to the contribution made by the tissues of the acclimatized which are cooled to a greater degree. Carlson, Young, Burns and Quinton,[12] after finding in their short experiments that the oxygen consumption was greater in the unacclimatized and the total heat loss and the rectal temperatures were the same as in the acclimatized, concluded that the size of the contribution of heat made in this way was what distinguished the acclimatized subjects. It would appear that this contribution may be comparatively small. Horvath and Golden[17] found in experiments which covered a wide range of exposure that the heat debt was incurred during the first 10 minutes. In our own experiments the tissue temperature changes in the forearm also indicate that the adjustment is made fairly rapidly, and the contribution which was made by tissue subjected to greater cooling by the increased venous drainage from the exposed parts must have been relatively small. The continued maintenance of an enhanced peripheral circulation in the acclimatized must, of course, be dependent on other mechanisms.

There is no evidence available to support the suggestion that, under conditions where the cold exposure is great enough to cause a fall in rectal temperature, the acclimatized have more efficient control of heat loss from sites other than the extremities. There is, however, evidence which indicates that there is greater heat production by the acclimatized. Our own results show an elevation of the basal metabolic rate in the Eskimos studied and Gottschalk and Riggs[18] found an increase in the serum protein-bound iodine in the same group. Newburgh and Spealman[19] reported a slow increase in basal metabolic rate in white men living in light clothing at a temperature of 15 C., and Horvath, Freedman and Golden[20] found an increase in sitting oxygen consumption in their white subjects who spent eight days in a room at −29 C. dressed in suits which had an insulative value of 3 to 4 clo. The animal experiments of Ring[21] and of Sellers and You[22] have also yielded evidence of increased oxygen consumption under basal conditions following long-term exposure to cold. The evidence concerning oxygen consumption during acute exposure is conflicting. Carlson, Young, Burns and Quinton[12] found a greater oxygen consumption in the unacclimatized during a short exposure to temperatures

−8 C. to −32 C. of men dressed in suits which "provided adequate insulation at −10 C. (Caloric loss equals basal metabolism plus 30 per cent)". Balke, Cremer, Kramer and Reichel[1] found no difference in oxygen consumption in their subjects during 20 minutes in a 20 C. bath after a four-week exposure which was very moderate in degree. Unfortunately we have no data in our own experiments on the oxygen consumption of our two groups of subjects during acute exposure. The animal work, however, is clear cut. Sellers, Reichman, Thomas and You[23] found that exposure to cold for four to six weeks led to an increased ability to maintain a high level of heat production during acute severe cold exposure, and this has been confirmed by Blair.[24]

The results now reported are consistent with the hypothesis that heightened thyroid activity plays a role in the increased heat production which we consider to be a feature of acclimatization to cold. For one thing, the pattern of the changes in the peripheral circulation which we have noted in the Eskimo is similar to that seen in hyperthyroidism. In the Eskimo, who has been exposed repeatedly to the cold, there is an increased skin temperature over hand and forearm with an increased blood flow to these same parts, and the spontaneous fluctuations which are seen in hand and forearm blood flow are greater. In cases of hyperthyroidism there have been demonstrated increased blood flow in the hand,[25] increased forearm blood flow,[26] increased blood flow through the skin[27] and increase in the spontaneous fluctuations seen in peripheral blood flow.[28] The increase in blood volume which is now reported is another suggestive point. In hyperthyroidism it is known that there is an increase in blood volume,[29, 30] and for corresponding basal metabolic rate values the increase in blood volume observed in hyperthyroidism has been reported to be approximately the same as that observed in the Eskimo.[31] Finally, the increased basal metabolic rate which we have found in our group of Eskimos points to increased thyroid activity, and the supporting work of Gottschalk and Riggs[17] on the same group of Eskimos has been noted.

There is also support for this hypothesis in animal work. Thyroid hyperplasia has been seen in the rat after prolonged cold exposure,[32] and Sellers and You[22] have found evidence of increase in thyrotrophic activity of the pituitaries of rats exposed more than two weeks to 1.5 C. Sellers and You[22] also found that survival of rats in the cold was prejudiced by thyroidectomy or the administration of propylthiouracil, and that anesthesia, calculated to abolish the heat contribution made by increased muscle tone, did not abolish the increased oxygen consumption at 30 C., which is one of the characteristics of rats exposed for two or more weeks to the cold. The same workers have gone on to demonstrate increased oxygen consumption and succinoxidase activity of liver tissue in rats after exposure of rats to cold for more than 16 days.[33] Scott, Thomas and Sellers[34] have further emphasized the importance of the increased rate of metabolism of visceral tissues by demonstrating that the electrical activity of the thigh muscles of acclimatized rats was lower both at 2 C. and 30 C. than was that of normal nonacclimatized animals. It is interesting in this connection that a surprising incidence of hepatomegaly has been noted in the Eskimo and that in rats exposed to the cold there is also enlargement of the liver.[35] You and Sellers[32] have also reported enlargement of the liver after exposure of rats to the cold. Baker and Sellers,[36] continuing their work on the metabolism of cold acclimatization, have found that the glycogen content of the heart, liver, diaphragm and of fat from perirenal and interscapular regions of the rat acclimatized to cold is reduced as compared with the unacclimatized animal. The blood sugar levels and the glycogen content of the skeletal muscles were unchanged. Cold acclimatized rats also show increased insulin sensitivity.

Though it is our conclusion that heightened thyroid activity has a role in the increased metabolic heat production which is a feature of cold acclimatization, it is not our belief that an increase in the secretion of the thyroid hormone is necessarily the sole agent responsible. The work of Ring[21] showed that the effect of thyroxin consisted of more than its direct

effect on basal metabolism. He found that the calorigenic response to epinephrine was potentiated by thyroxin, as was the maximum calorigenic response to cold. After prolonged cold exposure of rats he found the calorigenic effect of epinephrine to be about what would be expected from an equivalent increase in basal metabolism caused by thyroxin administration. It was his conclusion that epinephrine may account for 10 per cent of the increased metabolism produced by cold. There is also to be considered the suggestive work of Sellers and his group.[37] They found that adrenalectomy reduced the survival time in the cold of both acclimatized and nonacclimatized rats, and that nonacclimatized animals survived longer in the cold when they were pretreated with a combination of thyroxin and cortisone than they did when pretreated with either of these alone. At the present time, it can only be said that increased thyroid activity plays a part in the complex metabolic adjustments which take place during prolonged exposure to cold.

Summary

In a group of Eskimos in the Canadian Eastern Arctic who still live in a fashion which exposes them to severe cold, it was found that the forearm skin temperature and the forearm and hand blood flow were greater at rest in a room at 20 C. than they were in a control group of medical students. During immersion of the hand and forearm in water baths at temperatures of 5 to 42.5 C., the Eskimos always maintained higher blood flows in hand and forearm than did the control group. In the colder baths the forearm muscle temperature of the Eskimos fell more than it did in the controls, but this is believed to be due to greater blood flow through the exposed hand and the resulting increased cooling of deep tissues by the venous return. The evidence is that the contribution made to the total thermal requirements of the body by the cooling of deep tissues was small.

Exposure of the hand and forearm to cold caused a greater elevation of blood pressure in the Eskimos than in the white men. There was also a difference in the pain perceived by the two groups. The Eskimos reported less severe pain, and pain for a shorter period, than did the controls.

The experiments on peripheral blood flow suggested an increased heat production in the Eskimos, and an average elevation of basal metabolic rate of approximately 30 per cent was found. There was also an elevation of both plasma volume and total red cell volume. Review of our own data and of other reports in the literature provides support for the view that increased thyroid activity is a feature of the response to long term exposure to cold and that the increased thyroid activity determines the pattern of the vascular adjustments which are made.

Sumario Español

Se ha encontrado que la circulación de la mano y el antebrazo del esquimal es mayor que la de un grupo control de personas blancas en un clima templado tanto durante el descanso como a una temperatura ambiente de 20° C. y durante la exposición aguda al frío. Durante el esfuerzo al frío, la temperatura rectal fué mejor mantenida en el esquimal, aunque algunas temperaturas de músculo profundo bajaron más que en las personas blancas debido a la mayor circulación de las partes expuestas. Los esquimales mostraron una elevación del metabolismo basal y del volumen total del plasma y eritrocitos. Hay similaridades entre los cambios circulatorios encontrados en el esquimal y aquellos encontrados en hipertiroidismo.

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Long-Term Anticoagulant Therapy

Further Experiences

By JOHN TULLOCH, M.D., M.R.C.P. (Ed.), AND IRVING S. WRIGHT, M.D.

Experience with long-term anticoagulant therapy during the past seven years has been summarized. This report is based on the records of 227 individuals treated as private or outpatient clinic patients for from four weeks to seven years. Where adequate laboratory facilities are available outpatient long-term therapy may be satisfactorily controlled by physicians familiar with the use of anticoagulant drugs. Their correct use will lessen the incidence of thromboembolic episodes in patients who have previously suffered from such complications.

THE POSSIBILITY of long-term prophylactic and therapeutic use of anticoagulant therapy was a natural sequence to its successful use for acute thromboembolic conditions. This necessitated a marked revision in both the technical and the philosophic approach toward such conditions as recurrent thrombophlebitis, myocardial infarction and hearts in auricular fibrillation which were delivering multiple emboli and numerous additional conditions. From a static and resigned approach in which patient and physician alike awaited with apprehension the possibility of a series of serious or even fatal developments, it was conceivable that a dynamic attack might be at least considered with both physiologic and psychologic advantages.

In 1946, one of us[1] reported a preliminary experience with the use of Dicumarol in the long-term management of patients with rheumatic heart disease with auricular fibrillation and multiple emboli. It is of interest to record that one of the first patients, a woman who had suffered from 21 recognized emboli prior to anticoagulant therapy, is still alive and active. She was placed on anticoagulant therapy on Nov. 6, 1946, after having had nine emboli to different parts of her body in the previous 10 days. The only embolus which has been recognized since that date occurred in June, 1950, after 30 days of abstinence from Dicumarol, the only break in her therapy. This was a saddle embolus to the aortic bifurcation which fortunately disintegrated and descended into the smaller vessels with no ensuing loss of tissue. She resumed anticoagulant therapy and has continued it to date.

In the next year, Nichol and Fassett[2] reported their experience with long-term therapy in an attempt to forestall acute myocardial infarction. Additional experience confirming the original reports has subsequently been published by our group and others.[3-8]

While data regarding such long-term therapy are difficult to evaluate because of the countless variables introduced by the active lives of the individuals, the impression has been that the course of individuals so treated has been favorably affected. It has been clearly demonstrated that long-term anticoagulant therapy is feasible for ambulatory patients in active life, and that such patients can, in many instances, be self-supporting and productive citizens.

With the passage of years, additional experience with such patients in private practice and in the New York Hospital Anticoagulant Clinic appears to warrant a summary at this time.

MATERIAL AND METHODS OF STUDY

This report is based on the case records of 227 patients who have been treated with anticoagulant drugs (Dicumarol and Tromexan) on an outpatient basis for a period of four weeks or longer.* Long-

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* This analysis included experience up to Jan. 1, 1952.

term therapy of the patients included in this series was first begun in 1946. A few of these original patients are still under treatment eight years later. Ninety-nine patients have been cared for in the Anticoagulant Clinic of the New York Hospital, and 129 in private practice. One was treated privately initially and later attended the hospital outpatient clinic. The over-all experience thus obtained in the outpatient management of subjects receiving anticoagulant drugs totals 180 years, 124 days. One hundred and eighty-two subjects received Dicumarol during a total of 161 years, 339 days (59,104 days), while 53 subjects received Tromexan during 18 years, 173 days, (6,743 days). Eight subjects received both drugs at differing stages during their treatment.

The conditions treated and the number of patients in each group are shown in table 1, while the distribution of the cases between hospital and private practice is shown in table 2. A minimum of 546 thromboembolic episodes (table 3) had been experienced by 219 patients (the eight patients with glaucoma had not experienced any thromboembolic upset). In 258 instances the episode or episodes occurred just prior to the commencement of treatment, and in 288 instances these episodes antedated treatment, frequently by many years, and occurred during a minimum total of 549 years. Thirteen patients (five with thrombophlebitis, six with rheumatic heart disease, one with a cerebral thrombosis, and one with essential polyangiitis) were accepted for treatment, not because of a recent acute thromboembolic incident, but because of a history of past thromboembolic incidents. Eight patients with effort pain, or more severe coronary insufficiency were treated in the hope of preventing the development of a myocardial infarct. Six of these had previously had one or more myocardial infarcts. In all cases chosen for treatment the object was to prevent the occurrence of further thromboembolic episodes.

TABLE 1.—*Total Number of Cases Treated with Anticoagulant Drugs, on an Outpatient Basis, and the Total Duration of Treatment*

	Total Cases	Duration of Treatment in Days
Rheumatic heart disease with peripheral and pulmonary emboli	38	20,341
Thrombophlebitis	117	22,824
Myocardial infarction and myocardial ischemia	32	13,710
Glaucoma	8	636
Arterial thrombosis and embolism (excluding cerebral thrombosis)	9	2,740
Cerebral thrombosis	7	2,786
Thrombosis of central vein of retina	4	187
Thromboangiitis obliterans	6	736
Pulmonary embolism	3	940
Miscellaneous*	3	924
Total	227	65,824

Total duration of treatment in years: 180 years, 124 days

* Recurrent leg ulcers, 1 case; Essential polyangiitis, 1 case; Rupture of vein in calf, 1 case.

TABLE 2.—*Distribution of Cases Between Hospital and Private Practice*

	Hospital Practice		Private Practice	
	Total Cases	Duration of Treatment in Days	Total Cases	Duration of Treatment in Days
Rheumatic heart disease	30*	16,415	9*	3,926
Thrombophlebitis	39	8,345	78	14,479
Myocardial infarction and myocardial ischemia	4	1,671	28	12,039
Glaucoma	8	636	0	0
Arterial thrombosis and embolism	4	1,313	5	1,427
Cerebral thrombosis	3	353	4	2,433
Thrombosis of central vein of retina	4	187	0	0
Thromboangiitis obliterans	4	576	2	160
Pulmonary embolism	3	940	0	0
Miscellaneous	0	0	3	924
Total	99	30,436	129	35,388

* One patient is included in both the hospital and private group.

The patients selected were all intelligent, cooperative subjects who realized the importance of conscientiously taking the daily dose of drug prescribed for them, and also the necessity for the regular estimation of the prothrombin time. Lack of cooperation on the part of the patient was an indication for the cessation of treatment.

In general the prothrombin time of each patient was estimated once weekly. However, at the start of the outpatient management this was sometimes done twice or even three times weekly, while later, after the patient had been treated for some months and the dosage was stabilized, the interval between prothrombin estimations was increased in a few to 10 or 14 days or, rarely, longer. At each visit the patient was questioned and was examined, if this was indicated. After determination of the prothrombin time, the dosage schedule of Dicumarol or Tromexan for the next one or two weeks was determined.

TABLE 3.—*Incidence of Thromboembolic Episodes Prior to Treatment with Anticoagulant Drugs*

Condition Treated	Thromboembolic Complications							
	Thrombophlebitis	Pulmonary Embolism	Myocardial Infarction	Arterial Thrombosis and Embolism	Cerebral Thrombosis	Thrombosis of Central Vein of Retina	? Heart Attack	Total
Rheumatic heart disease	2	29	1	79	—	—	—	111
Thrombophlebitis	288	55	4	4	—	—	1	352
Myocardial infarction	—	—	35	4	—	1	—	40
Arterial thrombosis and embolism	—	1	4	11	—	—	—	16
Cerebral thrombosis	—	—	—	—	10	—	—	10
Thrombosis of central vein of retina	—	—	—	—	—	4	—	4
Thromboangiitis obliterans	3	—	—	1	—	—	—	4
Pulmonary emboli	—	4	3	—	—	—	—	7
Miscellaneous	2	—	—	—	—	—	—	2
Total	295	89	47	99	10	5	1	546

Prothrombin estimations were done in the laboratory by the Quick method, using rabbit lung as the source of thromboplastin. Normal results vary between 14 and 16 seconds. In the majority of patients treated in this series, a prothrombin time of 25 to 30 seconds was considered therapeutically desirable. In some 20 to 25 seconds was selected for a variety of specific reasons.

The following points have been determined from the records of each patient: (1) total duration of outpatient treatment; (2) amount of anticoagulant drug used; (3) average daily dose of the anticoagulant drug; (4) number of weeks in which the patient's prothrombin time was (a) less than 20 seconds, (b) between 20 and 24.9 seconds, (c) between 25 and 39.9 seconds, and (d) over 40 seconds; (5) complications resulting from the original disease process or from the treatment with the anticoagulant drugs, and the management of these complications; (6) the management of the problem of oral surgery. All deaths have been analyzed as to cause and as to their possible relationship to the anticoagulant therapy.

Forty-six of the 227 patients were treated as outpatients on two or more occasions, their outpatient course being interrupted by admission to the hospital for some reason, for example the development of a thromboembolic incident, the onset of congestive heart failure, the necessity for an operation, or for oral surgery, and other causes. Thirty-two patients had two periods of outpatient treatment, eight had three periods, five had four periods, and one had five periods. Although in some patients the anticoagulant drugs were continued throughout their stay in the hospital, each period of outpatient management has been analyzed separately. There are, therefore, 293 separate periods of outpatient anticoagulant treatment for analysis. In fifteen instances the interval between one hospital admission and the next was less than 28 days, but these periods have been included in the analysis. Details are given in table 4. Twelve subjects have been treated continuously for periods of more than 1000 days. The longest single period of treatment is 1670 days in a patient with rheumatic heart disease.

TABLE 4.—*Number of Periods of Outpatient Treatment Analyzed and Their Duration*

Days of Outpatient Treatment	Condition Treated									
	Rheumatic Heart Disease	Thrombophlebitis	Myocardial Infarction & Myocardial Ischemia	Glaucoma	Arterial Thrombosis & Embolism	Cerebral Thrombosis	Thrombosis of Central Vein of Retina	Thromboangiitis Obliterans	Pulmonary Embolism	Miscellaneous	Total
Under 28*	8	2	1	0	0	0	1	2	1	0	15*
28–49	12	25	3	1	2	2	2	2	1	0	50
50–99	13	38	9	4	2	3	1	3	1	0	74
100–199	11	30	5	3	2	0	0	0	1	1	53
200–299	10	17	2	0	2	1	0	0	0	1	33
300–399	9	10	6	0	1	0	0	1	2	0	29
400–499	3	1	4	0	0	0	0	0	0	0	8
500–599	0	3	1	0	1	0	0	0	0	1	6
600–699	2	3	0	0	0	1	0	0	0	0	6
700–799	1	1	3	0	1	0	0	0	0	0	6
800–899	0	0	0	0	0	0	0	0	0	0	0
900–999	0	1	0	0	0	0	0	0	0	0	1
1000–1499	4	1	4	0	0	1	0	0	0	0	10
1500–1999	2	0	0	0	0	0	0	0	0	0	2
Total	75	132	38	8	11	8	4	8	6	3	293

* These periods of less than 28 days have been included as a number of patients treated on more than one occasion as outpatients had only a short period of treatment between two hospital admissions.

OBSERVATIONS

Average Dosage and Inter- and Intraindividual Variations

A total of 3087.1 Gm. of Dicumarol was taken by 182 patients in 59,104 days, giving an average daily dose for all patients of 52 mg.

TABLE 5.—*Average Daily Dose of Dicumarol during 245 Periods of Outpatient Treatment in 182 Patients*

Daily Dose of Dicumarol in Mg.	Condition Treated										Total
	Rheumatic Heart Disease	Thrombophlebitis	Myocardial Infarction & Myocardial Ischemia	Glaucoma	Arterial Thrombosis and Embolism	Cerebral Thrombosis	Thrombosis of Central Vein of Retina	Thromboangiitis Obliterans	Pulmonary Embolism	Miscellaneous	
10–19	0	1	0	0	0	0	0	0	0	0	1
20–29	4	4	1	0	1	1	0	0	1	0	12
30–39	15	11	7	2	0	1	1	0	1	0	38
40–49	17	20	3	3	1	1	1	0	0	1	47
50–59	13	20	4	1	2	3	0	1	1	2	47
60–69	16	19	4	1	3	1	1	1	2	0	48
70–79	5	11	4	1	1	1	0	0	1	0	24
80–89	2	6	5	0	1	0	1	1	0	0	16
90–99	1	1	1	0	0	0	0	0	0	0	3
100–109	1	0	1	0	0	0	0	0	0	0	2
110–119	0	5	0	0	0	0	0	0	0	0	5
120–129	0	2	0	0	0	0	0	0	0	0	2
Total...											245

There was considerable interindividual variation in the average daily requirement of the drug. This is illustrated in table 5, from which it will be seen that the majority of patients required an average of between 40 and 69 mg. of Dicumarol per day. The extremes of dosage, however, ranged from an average of 19 mg. per day to an average of 124 mg. per day. Some patients when treated over a long period did vary in their intraindividual average daily requirement at different stages. However, the majority of patients who received two or more courses of outpatient treatment showed closely comparable average daily requirements for these courses, for example, one patient received 57, 53, 60 and 56 mg. as a daily average during four periods of treatment, while another received 29, 28, 27 and 31 mg. of Dicumarol also during four periods. On the other hand, a few patients did differ markedly in their average daily requirement from one course to the next. For example, one patient treated during two periods required a daily average of 113 mg. of Dicumarol during the first period and 79 mg. during the second. It is difficult in retrospect to explain this difference.

TABLE 6.—*Average Daily Dose of Tromexan during 56 Periods of Outpatient Treatment in 53 Patients*

Daily Dose of Tromexan in Mg.	Condition Treated					Total
	Rheumatic Heart Disease	Thrombophlebitis	Myocardial Infarction & Myocardial Ischemia	Arterial Thrombosis & Embolism	Thromboangiitis Obliterans	
100–199	0	0	0	0	0	0
200–299	0	5	0	0	2	7
300–399	0	7	1	0	0	8
400–499	0	11	3	0	1	15
500–599	0	6	0	0	0	6
600–699	1	6	2	0	0	9
700–799	0	1	1	2	2	6
800–899	0	1	1	0	0	2
900–999	0	1	2	0	0	3
Total.....						56

A similar variation in dosage requirement was noted for Tromexan. Fifty-three subjects received a total of 3502.4 Gm. of Tromexan in 6,743 days, giving an average daily requirement of 519 mg. The interindividual variation in average daily requirement was almost as great as with Dicumarol, ranging from 254 to 958 mg. (table 6). The distribution of cases over this range was more even than with Dicumarol.

Adequacy of Treatment

In spite of the variations just referred to, the adequacy of the anticoagulant treatment is reflected in the analysis of the prothrombin times recorded for each patient and in the incidence of thrombotic or embolic complications. As previously stated, the results of the prothrombin times have been grouped into four grades for analysis. A time of 25 seconds was considered to be the lower limit at which the anticoagulant treatment would be optimal. Prolongation of the prothrombin time to between 20 and 24.9 seconds was possibly adequate under most circumstances, but might not give maximum protection from thromboembolic complications. A prothrombin time of less than 20 seconds was considered to be therapeutically inadequate and to afford little

TABLE 7.—*Number of Weeks in which the Prothrombin Time is within the Four Specified Ranges of (a) Less than 19.9 Seconds (b) 20 to 24.9 Seconds (c) 25 to 39.9 Seconds and (d) Over 40 Seconds. This Does Not Correspond to the Total Duration of Treatment Recorded in Table 1, as in Many Patients the Prothrombin Time Was Not Estimated at Weekly Intervals*

	Prothrombin Time in Secconds			
	Under 19.9	20–24.9	25–39.9	Over 40
Dicumarol treated cases	1140 wks.	2069 wks.	3734 wks.	470 wks.
Tromexan treated cases	301 wks.	249 wks.	253 wks.	47 wks.
Total	1441 wks.	2318 wks.	3987 wks.	517 wks.

protection to the patient. At the other extreme a prothrombin time of over 40 seconds gave little or no additional protection as compared with 25 to 39 seconds and was undesirable owing to the risk of hemorrhagic complications. Details of the total duration in weeks in which the prothrombin time was at each level are given in table 7. It will be seen that a satisfactory prolongation of the prothrombin time was maintained more steadily with Dicumarol than with Tromexan.

Complications

Complications did occur, both of a thrombotic and hemorrhagic nature. Twenty-six out of 227 patients (11.4 per cent) experienced a total of 40 definite or possible thromboembolic episodes, while 43 patients (18.9 per cent) suffered 70 hemorrhagic complications. In addition, 33 subjects (14.5 per cent) developed a very high prothrombin time (well over 40 seconds) on 51 occasions without the occurrence of bleeding.

Thromboembolic Complications. These developed in four groups of patients: those with thrombophlebitis, myocardial infarction, pulmonary emboli, and rheumatic heart disease with emboli. Details are given in table 8. In 18 of the 40 incidents, an exact diagnosis could not be reached, but the incident was thought to represent a thrombotic or embolic episode. In 13 instances the prothrombin time was estimated on the day of the episode, and in 14 this was done within one to five days prior to the occurrence of the complication. In the remaining instances this information is not available. Details are given in table 9. If the figures for the two parts of the table are combined, it will be seen that as many as half of the thromboembolic complications[13] occurred while the prothrombin time was theoretically adequate to protect the patient against these episodes, and that three occurred while the prothrombin time was excessively prolonged. The diagnosis was not clear in 12 of these 16 episodes; there was considerable doubt in the mind of the physician in charge of the case as to the exact nature of the upset experienced by the patient. In one other instance a phlebitis was probably of a traumatic nature as it developed in the vein used for cardiac cathe-

TABLE 8.—*Incidence of Thromboembolic Complications Occurring during Treatment with Anticoagulant Drugs*

Thromboembolic Complications	Condition Treated				Total
	Thrombophlebitis	Rheumatic Heart Disease	Myocardial Infarction	Pulmonary Embolism	
Pulmonary infarct	0	2	1	0	3
? Pulmonary infarct	0	5	0	2	7
? Pulmonary and/or ? splenic infarct	0	3	0	0	3
? Splenic and/or ? renal infarct	0	1	0	0	1
? Renal infarct	0	2	0	0	2
? Mesenteric infarct	0	1	0	0	1
Thrombophlebitis	4	3	0	0	7
? Thrombophlebitis	3	3	0	0	6
Myocardial infarction	0	1	2	0	3
Cerebral embolism	0	1	0	0	1
? Cerebral embolism	0	1	0	0	1
Saddle embolus	0	1	0	0	1
Peripheral embolus	0	4	0	0	4
Total	7	28	3	2	40

TABLE 9.—*Thromboembolic Complications Occurring during Anticoagulant Therapy Correlated with the Prothrombin Time Estimated (A) on the Day of the Complication, and (B) One to Five Days Prior to the Occurrence of the Complication*

(A) Thromboembolic Complications	Prothrombin Time in Seconds				
	Under 19.9	20–24.9	25–39.9	Over 40	Total
Phlebitis	0	1	1	0	2
? Phlebitis	1	2	3	0	6
? Renal infarct	0	0	0	1	1
? Cerebral embolus	0	0	1	0	1
Pulmonary infarct	0	0	1	0	1
Peripheral emboli	1	0	0	0	1
Cerebral embolus	0	0	1	0	1
Total	2	3	7	1	13
(B)					
Phlebitis	1	0	0	1	2
Pulmonary infarct	1	1	0	0	2
? Pulmonary infarct	0	0	4	0	4
? Pulmonary and/or ? splenic infarct	0	0	1	0	1
? Renal and/or ? splenic infarct	0	0	1	0	1
Renal infarct	0	1	0	0	1
Myocardial infarct	1	1	0	0	2
? Mesenteric infarct	0	0	0	1	1
Total	3	3	6	2	14

terization one day following that procedure. Three definite episodes, phlebitis, pulmonary infarction and cerebral embolism, occurred at levels of prothrombin times of 31, 37 and 27 seconds, respectively. Five thromboembolic episodes, one of a doubtful nature, occurred when the prothrombin time was less than 20 seconds, and six episodes, two of which were of a doubtful nature occurred at prothrombin times of between 20 and 24.9 seconds. These findings indicate that at no level of prolongation of the prothrombin time was complete protection provided from thromboembolic episodes. When the prothrombin time ranged between 25 and 39.9 seconds, the episodes were often vague and not clearly of a thrombotic nature, but the majority of the episodes occurring when the prothrombin time was less than 24.9 seconds were quite definite. Nevertheless, even if doubtful, they were listed as thromboembolic complications. The 26 patients who sustained the 40 thromboembolic complications, had experienced a minimum of 78 indisputable episodes prior to the commencement of treatment. While all thromboembolic episodes occurred in patients receiving Dicumarol, it must be pointed out that the experience with Dicumarol was approximately nine times that with Tromexan.

Hemorrhagic Complications. A total of 70 episodes occurred in 43 patients (table 10). Many types of bleeding complications were encountered. Only cases of gross hemorrhage have been listed. No consistent search was made for microscopic hematuria. Subcutaneous ecchymoses and hematomata were the most common occurrences. In 60 instances the prothrombin time was estimated either on the day on which bleeding began or within two days before or after the onset of bleeding. The relationship of the bleeding to the prothrombin time is shown in table 11. The majority of these episodes occurred when the prothrombin time was over 25 seconds; 27 episodes when it was between 25 and 39.9 seconds and 19 when it was over 40 seconds. Only three patients showed evidence of bleeding when the pro-

TABLE 10.—*Hemorrhagic Complications Occurring during Outpatient Anticoagulant Therapy in 43 Patients*

Bleeding Site	Number of Cases
Ecchymoses	11
Hematomata	9
Hematuria	7
Epistaxis	6
Hemoptysis	6
Bleeding from hemorrhoids	6
Bleeding gums	5
Melena	4
Vaginal bleeding	3
Hematemesis	2
Excessive menstrual bleeding	2
Cerebral hemorrhage	2
? Intracranial bleeding	1
Bleeding into anterior chamber of eye	1
Acute hemorrhagic glaucoma	1
Traumatic hemarthrosis	1
Bleeding from tongue	1
Bleeding from forehead	1
Cut during shaving	1
Total	70

thrombin time was less than 20 seconds; in one of these three patients hematemesis occurred during a bout of acute gastritis, in one ecchymoses developed on the legs following trauma, and in one patient ecchymoses appeared spontaneously on the legs. Eleven episodes occurred when the prothrombin time was between 20 and 24.9 seconds. In these the prothrombin deficiency was not necessarily the sole factor responsible for the bleeding, for example, hematomata developed after injury and injection, and hematuria after catheterization. Only cerebral hemorrhage was of serious consequence in this group. It accounts for the sole death due to hemorrhage in patients still receiving anticoagulant drugs.

Taking the number of bleeding complications occurring respectively at prothrombin time between 25 and 39.9 seconds and over 40 seconds in relationship to the number of weeks in which the prothrombin time was known to be at these levels, 3987 and 517 weeks respectively, it is evident that, although bleeding may occur when the prothrombin time is between 25 and 39.9 seconds, it is relatively more common when the prothrombin time is over 40 seconds. Seven bleeding complications occurred in six patients receiving Tromexan; the remaining patients were receiving Dicumarol. This is approximately in proportion to the duration of treatment with the two drugs.

Treatment of the bleeding consisted in most cases in the adjustment or temporary cessation of Dicumarol (or Tromexan) administration until the bleeding had ceased. They were not stopped when the bleeding was slight and the prothrombin time low, for example, subcutaneous ecchymoses, slight bleeding from gums or hemorrhoids. Eleven patients received specific treatment to hasten the return of the prothrombin content of their blood to more normal levels. Two patients received vitamin K_1 and nine received water soluble vitamin K. Two of the latter nine patients were also transfused with whole fresh blood, receiving 500 cc. and 1500 cc., respectively.

High Prothrombin Time without Bleeding. A further feature encountered during the out-

TABLE 11.—*Prothrombin Time Determinations on the Day of Each Bleeding Complication or within the Limits of Two Days before and Two Days after the Onset of Bleeding, in the Absence of Treatment during that Period*

	Prothrombin Time in Seconds					
	Under 19.9	20-24.9	25-39.9	Over 40	Unknown	Total
Ecchymoses	2*	2*	4*	1*	2	11
Hematomata						
(a) after injury	0	1	1	0	1	3
(b) after injection	0	1	2	1	0	4
(c) spontaneous	0	1	1	1	0	2
Hematuria	0	2†	2	2	1	7
Epistaxis	0	0	3	2	1	6
Hemoptysis	0	2‡	2	1	1	6
Bleeding from hemorrhoids	0	1	4	0	1	6
Bleeding gums	0	0	2	2§	1	5
Melena	0	0	2	2	0	4
Vaginal bleeding	0	1	1	0	1	3
Hematemesis	1¶	0	1‖	0	0	2
Excessive menstrual bleeding	0	0	1	1	0	2
Cerebral hemorrhage	0	1	0	1	0	2
? Intracranial bleeding	0	0	0	1	0	1
Bleeding into anterior chamber of eye	0	0	1	0	0	1
Acute hemorrhagic glaucoma	0	0	0	1	0	1
Traumatic hemarthrosis	0	0	0	1	0	1
Bleeding from tongue	0	0	0	1	0	1
Bleeding from forehead	0	0	0	0	1	1
Cut during shaving	0	0	0	1	0	1
Total	3	11	27	19	10	70

* Following a blow in one case of each group.

† Following catheterization in one case.

‡ One case with slight hemoptysis for 1 month had a prothrombin time which gradually rose from 18.5 seconds (C 14.1) to 29 seconds (C 14.2) over the month.

§ One case showed variation in the prothrombin time during the 3 weeks of bleeding between 47 seconds (C 15.8), 28 seconds (C 14.8), and 51 seconds (C 15.5).

¶ Associated with acute gastritis.

‖ Associated with a hiatus hernia.

patient anticoagulant treatment was the occurrence of excessive prolongation of the prothrombin time without associated bleeding. This occurred in 33 patients on 51 occasions. Twenty-nine patients who were

receiving Dicumarol developed excessive prolongation of the prothrombin time on 46 occasions, while this developed five times in four patients who were receiving Tromexan. Again this incidence is in proportion to the duration of treatment with the two drugs. In these, as in the patients exhibiting bleeding, the Dicumarol (or Tromexan) was temporarily stopped until the prothrombin time had fallen to a safe level. On 23 occasions (21 related to Dicumarol administration, and two to Tromexan), treatment with water soluble vitamin K or vitamin K_1 was also given to hasten the fall in prothrombin time.

Administration of Vitamin K and Vitamin K_1. Twenty-four subjects were treated with water soluble vitamin K on 29 separate occasions, and five subjects received vitamin K_1 on six occasions. One patient was treated with both vitamin K and vitamin K_1 during one episode. Two patients were treated on more than one occasion; one patient was very unstable in this regard, receiving vitamin K on five separate occasions, and the other received vitamin K_1 on two occasions and vitamin K on a third. The indications for administration of either drug were, (1) an excessive prolongation of the prothrombin time without bleeding on 23 occasions; (2) bleeding on 11 occasions; (3) one episode finally recorded as renal infarction, or renal stone which produced bleeding with a prothrombin time of 51 seconds (control 16 seconds).

The bleeding episodes which were treated were as follows: Prolonged excessive menstrual flow (prothrombin time 46.6 seconds, 30 seconds, and 55 seconds during the three weeks prior to menstruation), intracranial bleeding (prothrombin time 41 seconds), ecchymoses (prothrombin time 16.2 seconds), hematemesis (prothrombin time 19.9 seconds), hematoma following injection (prothrombin time 38 seconds), bleeding from nose and gums (prothrombin time 98 seconds), cerebral hemorrhage and melena (prothrombin time 51 seconds), hematemesis and melena (prothrombin time 26 seconds), cerebral hemorrhage (only death from hemorrhage) (prothrombin time 24 seconds), acute hemorrhagic glaucoma (prothrombin time 78 seconds), and melena (prothrombin time 215 seconds). The last two conditions were treated with vitamin K_1.

In 21 patients water soluble vitamin K was given as a single intravenous injection, the effective dose ranging from 60 to 154 mg. One patient with hematemesis and melena from a hiatus hernia, received 72 mg. of vitamin K in a single intravenous injection and was transfused with 1500 cc. of fresh blood. In 12 instances the prothrombin time was estimated on the day following a single dose of vitamin K and in seven it had fallen to within the normal range (table 12).

The vitamin K_1 was given by mouth. The doses were 1.0 Gm. on three occasions, and 750 mg. on a fourth. In the fifth case the patient received 100 mg. at the onset and 500 mg. six and one-half hours later. One patient with acute hemorrhagic glaucoma who received 1 Gm. by mouth also received 72 mg. of vitamin K intravenously. In four of these patients the prothrombin time was estimated on the day following the vitamin K_1 administration and in all it was greatly reduced (table 12). It has been found in other studies that there is usually a marked reduction from an elevated prothrombin time within four to eight hours after the oral administration of

TABLE 12.—*Response of the Prothrombin Time Following One Dose of Water Soluble Vitamin K or Vitamin K_1*

Dosage of Water Soluble Vit. K or Vit. K_1	Prothrombin Time in Seconds	
Water Soluble Vitamin K	Before vit. K	Next day
mg. i.v.		
144	99.5	25
72	80	40
72	69	57.1
72	72.5	24
72	90	49
72	41	21.7
60	96	20.1
Vitamin K_1		
1 Gm. orally	196	30.2
1 Gm. orally	75	19.3
750 mg. orally	96.5	18

vitamin K_1, or vitamin K_1 oxide in doses of 100 to 500 mg.

Oral Surgery. Fourteen patients required extraction of teeth on 15 occasions. In 13 instances the patient's prothrombin time was allowed to return to normal or near normal before extraction was undertaken. Administration of Dicumarol was therefore stopped in each case several days before the oral surgery was to be undertaken; four days in most cases, but eight days in one patient. In three patients the prothrombin time on the day of the extraction was known; in two it was normal, and in the third it was 19 seconds (control 16 seconds). In the other cases, the prothrombin time recorded one to five days before the oral surgery was either near the normal level or in the low therapeutic range. No undue bleeding occurred in these cases. In one patient no opportunity for proper preparation was available and he had the high prothrombin time of 51 seconds (control 15.5 seconds) when extraction was performed. The tooth sockets oozed blood for three days. In one patient the details of Dicumarol dosage and of the prothrombin times are not known, but it was recorded that the tooth sockets were sutured and that there was no undue bleeding.

Potentially serious thromboembolic complications occurred in one of the patients in which the prothrombin time was allowed to return to normal before dental surgery; no Dicumarol had been taken for eight days. This patient suffered from rheumatic heart disease with auricular fibrillation and was receiving long-term anticoagulant therapy because of previous multiple emboli. Her experience illustrates the risk of further emboli when anticoagulant therapy is discontinued in these cases. The delay of eight days in undertaking the oral surgery was unexpected and unfortunate. In spite of restarting Dicumarol on the day on which the oral surgery was performed, a cerebral embolus developed after two days when the prothrombin time was 18.1 seconds (control 15.2 seconds), and four days later a second embolus lodged at the bifurcation of the right brachial artery (prothrombin time 18.3 seconds, control 13.7 seconds). Following adequate anticoagulant therapy, no further emboli occurred and these apparently disintegrated without serious residual.

Other Complications. Incidents of importance occurred in 19 patients during the course of their outpatient management. Seven were admitted to the hospital on 10 occasions for treatment of heart failure. Four patients were admitted for operations; two for mitral commissurotomy, one for a cholecystectomy, one for an exploratory laparotomy, and one was admitted with a renal calculus. Anticoagulant therapy was temporarily discontinued prior to each operation. No untoward complications developed in association with these episodes. A chalazion was excised from one patient after Dicumarol had been stopped for five days and while the prothrombin time was 16.5 seconds (control 15 seconds). A hyperkeratotic patch was removed from the hand of another patient by electrofulguration while his prothrombin time was 30.9 seconds (control 14.8 seconds). Two patients with menstrual irregularity were admitted for a diagnostic dilatation and curettage. This was carried out in each case after the prothrombin time had fallen to within the normal range. One pregnant woman was delivered without ill effect while her prothrombin time was 32 seconds. Two patients developed psychiatric disorders and Dicumarol administration had to be temporarily stopped because of the difficulty of controlling the therapy. One developed schizophrenia and the other a depressive state.

Comparison of Hospital and Private Outpatient Management

The respective merits of hospital and private outpatient treatment may be roughly assessed by comparing, (1) the number of weeks in which the prothrombin time was in each of the four grades previously described, and (2) the incidence of thromboembolic and hemorrhagic complications. Details of the distribution of the prothrombin times are given in table 13, and of the incidence of thromboembolic and hemorrhagic complications in table 14. There is no striking or statistically signifi-

TABLE 13.—*Comparison of Prothrombin Times Observed in Outpatients Treated in Hospital and Private Practice. Number of Weeks during which the Prothrombin Time Is within the Specified Ranges*

	Prothrombin Time in Seconds			
	Under 19.9	20–24.9	25–39.9	Over 40
Hospital cases.....	596	960	2392	331
Private cases.....	845	1358	1595	186

TABLE 14.—*Comparison of Incidence of Thromboembolic and Bleeding Complications in Outpatients Treated in Hospital and Private Practice*

	Thromboembolic Complications	Bleeding Complications
Hospital cases..	27 episodes in 16 patients	50 episodes in 30 patients
Private cases...	13 episodes in 10 patients	20 episodes in 13 patients
Total.....	40 episodes in 26 patients	70 episodes in 43 patients

cant difference between the two series. Many of the private patients traveled widely, and it was judged safer to maintain their prothrombin time between 20 and 25 seconds, rather than at a higher level.

Deaths

Twenty patients have died. Eleven were still receiving anticoagulant drugs at the time of death. In eight, treatment had been discontinued and in one case it is not known whether the patient was still taking Dicumarol or not. Of the patients still receiving Dicumarol, six were being treated because of rheumatic heart disease with emboli, two because of previous myocardial infarction, and one each because of pulmonary emboli, auricular fibrillation with arterial emboli, and hepatic vein thrombosis. The cause of death in these patients is listed in table 15.

The two patients who died suddenly had rheumatic heart disease, and, when last estimated, the prothrombin time of each had been within the therapeutic range (28.7 seconds, control 14.7 seconds, two days before death, and 30.5 seconds, control 15.5 seconds,

TABLE 15.—*Cause of Death in 20 Patients*

Condition Treated	Cause of Death															
	Congestive Heart Failure		Myocardial Infarction		Cerebral Vascular Accident		Liver Failure		Malignant Disease		Pneumonia		Sudden			
	*	†	*	†	*	†	*	†	*	†	*	†	*	†		
Rheumatic heart disease	3	2‡	1	1	0	1	0	0	0	0	0	2	0			
Myocardial infarction	0	0	1	0	1	0	0	0	0	0	0	0	0			
Pulmonary embolism	1	1	0	0	0	0	0	0	0	0	0	0	0			
Thrombophlebitis	0	0	0	0	0	0	1	0	0	2	0	0	0			
Cerebral thrombosis	0	0	0	0	0	0	0	0	0	0	1	0	0			
Arterial thrombosis and embolism	1	0	0	0	0	0	0	0	0	0	0	0	0			
	5	4	2	1	1	1	1	0	0	2	0	1	2	0		
	9		3		2		1		2		1		2			

* On anticoagulants at time of death.

† Off anticoagulants before death.

‡ Anticoagulant status of these two patients unknown.

six days before death, respectively). There was no reason to suspect from their previous course that these values were materially altered at the time of death. Three died in congestive heart failure in the hospital while being adequately treated with anticoagulants. The sixth patient with rheumatic heart disease died of myocardial infarction. The patient treated because of pulmonary emboli died in congestive heart failure. Two other patients died while in the hospital and on anticoagulant therapy; one with thrombosis of the hepatic veins died from liver failure, and the other, with auricular fibrillation and arterial emboli, died in congestive heart failure. Of the two patients who were being treated because of myocardial infarction and who died, one died from what was thought to be a fresh infarction. His prothrombin time on the day prior to death was not optimal, being 20 seconds (control 16 seconds). The other patient died of a cerebral hemorrhage. Two days before death, his prothrombin time

was 24 seconds (control 16 seconds). It is unlikely that the reduction in the prothrombin content of the blood was responsible for the initiation of the cerebral bleeding, but it undoubtedly contributed to the severity of the bleeding once this had occurred.

The cause of death in the eight patients dying after discontinuing anticoagulant treatment varied. Two patients who had been treated for phlebitis died of malignant disease; one had previously developed a hemiplegia. Two patients with rheumatic heart disease died in congestive heart failure. One patient died of a recurrence of myocardial infarction, and a second patient who had previously sustained a myocardial infarction developed a cerebral accident and died. One patient treated because of pulmonary emboli died in congestive heart failure, and one patient treated for a cerebral thrombosis died of pneumonia. The one patient in whom the anticoagulant status at the time of death is not known had been admitted to a hospital in psychotic state and her dosage was not known. She had advanced rheumatic heart disease, and died in congestive heart failure about two weeks after developing a pulmonary embolus.

Conclusions

1. Where adequate laboratory facilities are available, outpatient long-term anticoagulant therapy may be instituted by any physician familiar with the use of anticoagulant drugs.

2. Properly controlled outpatient anticoagulant therapy is relatively safe and will lessen the incidence of thromboembolic episodes in patients previously suffering from such complications.

3. Complete protection from thromboembolic incidents cannot be guaranteed during continuous treatment with anticoagulant drugs. Such episodes may occur at all levels of prothrombin time, as may hemorrhagic complications. Definite thromboembolic episodes are most liable to occur when the prothrombin time is less than 20 seconds, and hemorrhagic complications are most common when the prothrombin time is over 40 seconds. Minor trauma will induce local bleeding at any level of prolongation of the prothrombin time.

4. Vitamin K, and more particularly vitamin K_1, are of value in the treatment of the hemorrhagic complications associated with prolonged prothrombin times (diminished prothrombin activity in the blood).

5. Surgery may, in most instances, be undertaken with safety, by temporarily lowering the prothrombin time to near the normal level. There is some danger from thromboembolic complications in doing this in patients such as are discussed in this report. Therefore, the anticoagulant drugs should be resumed at the earliest possible time, preferably on the first or second postoperative day.

6. Deaths which occurred while anticoagulant drugs were being given were seldom related to the anticoagulant therapy. Only one death from hemorrhage occurred in this fairly extensive series of cases.

7. In consideration of the results herein reported, it should be remembered that only patients with severe heart or vascular disease who were suffering from recurrent thromboembolic complications were included (with the exception of eight cases with glaucoma). The risk of complications of many types inherent in such diseases was considered in the selection of these patients.

Summary

The case records of 227 patients who have been treated with anticoagulant drugs as outpatients for four weeks or more have been reviewed and analyzed.

Acknowledgment

Acknowledgement is made to Dr. William T. Foley for the use of certain records of his private patients which added to the total experience herein analyzed.

Sumario Español

La experiencia en la terapia a término prolongado con anticoagulantes se resume. Este informe esta basado en los protocolos de 227 individuos tratados como pacientes privados o como casos de clínica ambulatorios por un término de cuatro semanas a siete años. Donde existan facilidades de laboratorio

adecuadas el tratamiento ambulatorio a largo término puede ser satisfactoriamente controlado por médicos que estan familiarizados con el uso de los anticoagulantes. Su uso correcto reduce la incidencia de episodios tromboembólicos en pacientes que previamente han sufrido tales complicaciones.

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Cardiovascular Adaptations to Prolonged Physical Effort

By GEORGE L. BECKNER, M.D., AND TRAVIS WINSOR, M.D.

Studies of the cardiovascular system were made among 26-mile marathon runners after at least five years of physical training. Studies made with the subjects at rest showed an electrocardiogram characterized by a vertical or semivertical electrocardiographic position of the heart in the chest, bradycardia, high voltage of the QRS complexes and high T and U waves. T waves which were low with respect to the height of the R waves were not encountered. Etiologically the heart was enlarged. Immediately after running 26 miles the transverse diameter of the heart was decreased considerably.

THE RECOGNITION of the acute and chronic physiologic adaptations of the cardiovascular system which occur as a result of intensive, prolonged physical exertion is of importance because the changes which result are similar in many respects to those seen with disease. Barach,[1] Gordon, and coworkers[2] and Branwell and Ellis[3] have pointed out that cardiac enlargement is a usual finding among marathon runners and is not indicative of cardiac disease. The present study confirms this observation and illustrates certain electrocardiographic deviations from normal which resemble findings encountered in patients with cardiac disease. It is the purpose of this report to describe the acute and chronic changes occurring in the cardiovascular system as a result of prolonged physical exertion among well-trained marathon runners.

METHODS AND MATERIALS

One hundred and sixty-five male marathon runners with more than five years of physical training and 40 male nonrunners were studied. The average height of the runners was 68 inches (65 to 76) and of the controls 65.5 inches (59 to 71). The runners' ages averaged 27.9 years (18 to 48) and the controls' 25.5 years (18 to 42). The average weight of the runners was 142 pounds (119 to 168) and of the controls 148 pounds (162 to 175).

Studies were made before and after running 26, 18 or 10 miles on city streets during the day in an average temperature of 78 F. (70 to 90 F.) and humidity of 35 per cent (20 to 50). Studies made before the races were carried out usually from 1 to 24 hours prior to running and were repeated from one to five minutes after or in certain instances at longer periods up to 56 hours. The subjects of the control group consisted of males in sedentary occupations (airplane pilots) in an industry which required frequent physical examinations. Two hundred electrocardiograms were taken on the runners and 50 on the nonrunners. Forty tracings were taken with a string galvanometer* and the remainder with the Viso-Cardiette.† All electrocardiograms were taken with the patient in the prone position. The various electric axes of the electrocardiogram were analyzed in a similar manner in the two groups from amplitudes rather than area, with the aid of a hand lens when indicated. The amplitude of all waves was measured in millimeters and the duration in seconds. The electrocardiographic position of the heart in the chest was determined according to the method of Wilson and his coworkers.[4] The corrected Q-T interval was determined, using a modified Bazette formula as described by Taran and Szilagyi.[5] Venous pressures were recorded with the Phlebomanometer.[6] Electrolyte studies on blood samples drawn before and after the races were carried out by a well established commercial laboratory using standard technics.‡ The cardiac size of both groups was measured from teleoroentgenograms using the technics of Hodges and Eyster[7, 8] and Ungerleider and Gubner.[9] The transverse, broad, long and great vessel measurements were made directly from the teleoroentgenogram and the cardiac area was calculated from the formula $A = \pi/4 \times L \times B$.[7]

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* Cambridge Instrument Co., New York, N. Y.

† Sanborn Co., Cambridge, Mass.

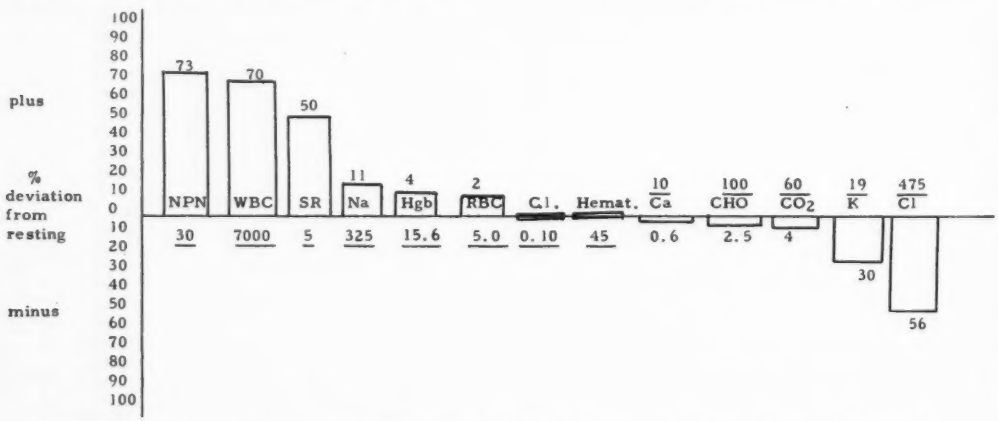
‡ Courtesy of The Clinical Laboratory, Hammack & Maner, Los Angeles, Calif.

Results

General Observations. The average weight loss for 40 runners running 26 miles was 5.1 per cent of the body weight; the average loss for eight runners running 18 miles was 3.4 per cent of body weight; while the average loss for 56 runners running 10 miles was 2.7 per cent of body weight. Although the weight loss was not linear the approximate loss was 1 per cent of body weight for each five miles run. The blood pressure in three runners averaged 126/75 before the race and 90/60 after the race. The antecubital venous pressures in 10 runners was normal before the race but after running averaged 210 per cent above the resting level. The pressures remained elevated for 30 minutes after running after which they returned to the resting levels. Abdominal compression resulted in a decrease in the venous pressure in all cases before and after the race. The pulse rate for the runners before the race averaged 57 beats per minute (40 to 72) and for the controls 65 beats per minute (55 to 85). After the race the pulse rate of the runners averaged 91 beats per minute (76 to 108).

Electrolyte changes occurring in 10 runners are shown in figure 1. Of particular interest are the great reduction in the blood chloride and the increase in blood nonprotein nitrogen. Five of the subjects with low blood chloride had muscle cramps soon after they stopped running; it was felt that the low blood chloride may have been responsible for these cramps. The serum potassium level after running did not deviate from the resting level significantly. There was no positive correlation between the increased height of the T waves in the electrocardiogram after exercise and the serum potassium encountered immediately after the race. The potassium level was followed for 8, 21 and 30 hours after running in two subjects. In these subjects the serum potassium rose above the values found immediately after the race and it was noted that as the serum potassium rose the T waves became smaller.

Electrocardiographic Findings. The electro-



NPN = non protein nitrogen (mg.)
WBC = white blood count
SR = sedimentation rate Wintrobe (mm. 1 hr.)
Na = serum sodium (flame photometer) (mg. %)
Hgb = hemoglobin (spectrophotometry) (Gm.)
C.I. = color index
Hemat. = hematocrit Wintrobe (%)
Ca = serum calcium (mg. %)
CHO = blood sugar (mg. %)
CO_2 = carbon dioxide combining power (volume %)
K = serum potassium (flame photometer) (mg. %)
Cl = serum chloride (mg. %)

FIG. 1. Effect of running 26 miles on the blood chemistry of 10 runners. The average resting values are shown in the underlined figures and the percentage deviation from the resting value is shown in the open figures. The low serum chloride could be correlated with the presence of muscle cramps which occurred after the race.

TABLE 1.—*Amplitude and Duration of P waves in Lead II. The Runners Show Normal P Waves at Rest, but These Are High and Wide after Running.*

	Nonrunners		Runners			
			Before		After	
	Amp.	Duration	Amp.	Duration	Amp.	Duration
Mean.....	1.0	0.090	1.2	0.086	2.0	0.093
Min.....	0.0	0.070	0.25	0.060	0.5	0.080
Max.....	2.0	0.120	2.0	0.120	4.0	0.120
S.D. ±....	0.40	0.015	0.47	0.007	0.50	0.009
C.V. ±%..	40.0	16.0	39.0	8.0	25.0	9.0

C.V. = Coefficient of variation.

cardiographic position of the heart in the chest before and after the race was determined: In 94.3 per cent the position was semivertical or vertical before and after the race. In 5.7 per cent the position was intermediate before and after the race. In no instance was the position horizontal or semihorizontal.

The amplitude and duration of the P waves in lead II were studied in the two groups (table 1). P waves of normal height and duration were present in the nonrunners and in the runners before the race, but after the race these waves increased an average of 66.6 per cent in amplitude and 8.1 per cent in duration. The average magnitude of the electric axes of the P waves for the two groups at rest was 1.3 and 1.3 units, respectively, and the average direction 50 degrees and 50 degrees, respectively. After running, the average magnitude increased 61 per cent to 2.1 units, and the direction moved to the right 15 degrees, to 65 degrees. An increase in the magnitude of the P wave vector similar to that which occurred in the runners after exercise was not produced in three normal subjects by holding the breath in deep inspiration.

The P-R interval of the runners at rest averaged 0.16 second (0.14 to 0.20) and of the nonrunners 0.17 second (0.15 to 0.21). After running, the P-R interval decreased or showed no change except in one runner whose P-R increased from 0.16 to 0.21 second (fig. 2).

The duration of the QRS complexes in lead II was compared in both groups. The average for the runners at rest was 0.086 second (0.070 to 0.100, S.D. 0.011) as compared with 0.074 (0.050 to 0.100, S.D. 0.017) for the nonrunners. After running, the duration was less than the resting value in all cases.

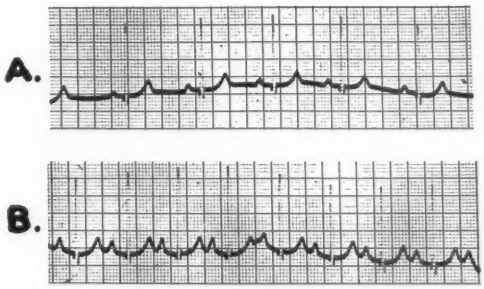


FIG. 2. Lead II, before and after running: (*A*) Before exercise, showing P waves of normal size and shape with a P-R interval of 0.16 second. (*B*) After exercise, showing P waves of increased amplitude with P-R interval measuring 0.21 second.

The direction and magnitude of the mean electric axes of the QRS complexes of the nonrunners and runners were determined. The average direction for the nonrunners was 54 degrees (30 to 102) as compared with 66.8 degrees (−5.0 to 95.0) for the runners before the race. After the race the average was 69.1 degrees (−5.0 to 69.0). The magnitudes of the nonrunners averaged 9.0 units (2.3 to 16.7); those for the runners before the race averaged 14.1 units (7.6 to 39.0). After the race the average magnitude was 15.2 units (6.5 to 38.5). Thus the direction of the axis of the QRS complexes was more to the right and the magnitude

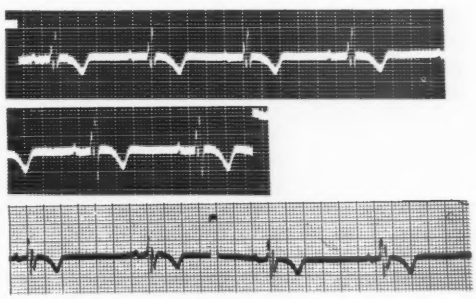


FIG. 3. V_1 leads taken at rest from three different runners showing R-R prime waves which suggest the possibility of a right bundle branch block. These changes persisted over a period of five years.

TABLE 2.—*Amplitude of R Waves in Lead II among Runners and Nonrunners. R Waves are High among the Runners at Rest and Increase Slightly after a 26 Mile Run.*

	Nonrunners	Runners	
		Before	After
Mean	12.0	16.2	17.9
Min	3.6	9.0	9.0
Max	22.0	40.0	37.0
S.D. ±	5.0	6.5	7.0
C.V. ±%	41.6	39.0	38.0

was greater in the runners at rest than in the nonrunners. Running resulted in a further increase in magnitude with a slight additional shift to the right. In three normal subjects electrocardiograms were taken with the breath held in inspiration. The magnitude of QRS did not approach the values in the runners at rest.

The configuration of the QRS complexes in V_1 was within normal limits in all the 165 runners except the three shown in figure 3. In these there was an R-R prime wave suggestive of a right bundle branch block although the width of the QRS complexes did not exceed the upper limit of normal (0.1 second). These complexes were seen before and after running and were observed at intervals for a period of five years.

The amplitude of the R waves in lead II for the runners at rest averaged 16.2 mm. with a 10.5 per cent increase after running (table 2). This average amplitude was considerably greater than that of the nonrunners which was 12.0 mm. Eighteen per cent of the runners had R waves in lead II which exceeded the maximum (22.0 mm.) of the nonrunners.

TABLE 3.—*Amplitude of the Highest R Waves in the 6 Precordial Leads. Ten Per Cent of the Resting Tracings of the Runners Exceeded the Maximum Values for the Nonrunners.*

	Nonrunners	Runners	
		Before	After
Mean	18.6	24.1	25.8
Min	8.0	8.0	4.0
Max	31.0	52.0	42.0
S.D. ±	5.1	8.0	7.0
C.V. ±%	26.0	33.0	27.0

TABLE 4.—*Deepest S Waves in Precordial Leads (Usually Lead V_2). Twelve Per Cent of the Runners Had S Waves which Exceeded the Maximum Value for the Nonrunners.*

	Nonrunners	Runners	
		Before	After
Mean	12.7	19.8	21.7
Min	0.0	4.0	2.0
Max	29.0	38.0	45.0
S.D. ±	5.3	4.5	8.0
C.V. ±%	41.0	23.0	36.0

The highest R waves of the six precordial leads for nonrunners and runners is shown in table 3. The tallest R waves occurred in V_4 in 72 per cent of the runners and in 70 per cent of the nonrunners. For the nonrunners the maximum R wave was 31.0 mm. Ten per cent of the tracings taken of the runners at rest exceeded this value. The average height of the R waves in the nonrunners was 18.6 mm. while in the runners at rest it was 24.1 mm., or an average increase of 29.5 per cent. After running, the mean height of the R waves increased 7.1 per cent.

The amplitude of the deepest S waves in the six precordial leads is shown in table 4. The deepest S wave of the runners at rest occurred in lead V_2 in 60 per cent; in V_1 in 20 per cent; and V_3 in 20 per cent with a similar distribution after running. Among the nonrunners the deepest S wave occurred in lead V_2 in 69 per cent; in V_1 in 11 per cent and in V_3 in 20 per cent. The average for the control group was 12.7 mm. whereas the average for the runners at rest was 55.9 per cent greater, being 19.8 mm. After running, the average increase in depth of the S wave over the resting tracing was 9.6 per cent. The maximum depth of the S waves for the nonrunners was 29.0 mm. This value was exceeded by 12 per cent in the tracings of the runners at rest (figs. 4 and 5).

The sum of the amplitudes of R + S of lead II is shown in table 5. The mean value for the nonrunners is 13.4 mm. while that for the runners at rest is 17.2 mm. (28.3 per cent greater). After running, the mean was 19.2 mm., an increase of 11.6 per cent over the resting value. The maximum R + S amplitude

for the nonrunners was 22.0 mm.; however, 15 per cent of the runners had R + S amplitudes at rest which exceeded this maximum value (fig. 6).

The greatest R + S voltage of the six precordial leads was studied by adding the height of the R wave to the depth of the S wave of the precordial lead showing the largest amplitude (table 6). Among the nonrunners the highest R + S wave amplitude occurred in V_1 in 40 per cent; in V_3 in 30 per cent; in V_2 in 20 per cent and in V_5 in 10 per cent of subjects. Among the runners both at rest and after the race the highest R + S amplitude

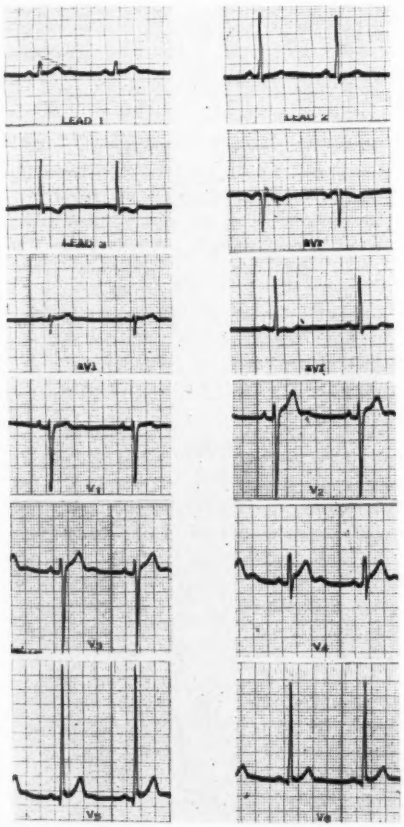


FIG. 4. Electrocardiogram of a marathon runner at rest recorded after five years of running in national 20 mile races. The slow cardiac rate, high voltage of the QRS complexes in the precordial leads and shift of the transitional zone to the left are prominent features of this tracing.

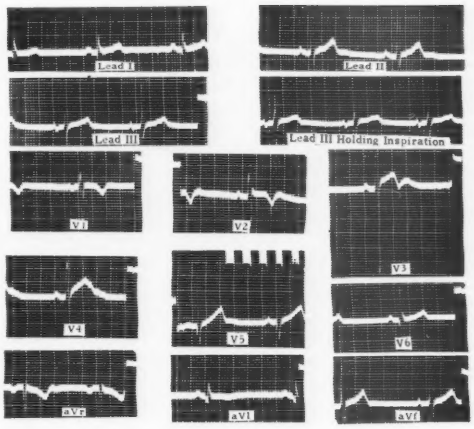


FIG. 5. Typical electrocardiogram of a marathon runner taken with the subject at rest. Deep S waves are seen in V_3. Sinus bradycardia is present. There is a large U wave of typical configuration in V_3 and notching on the downstroke of the T wave of V_4.

occurred in V_2 in 35 per cent; in V_3 in 30 per cent; and in V_5 in 5 per cent of subjects. The mean R + S amplitude for the nonrunners was 25 mm. while for the runners at rest it was 34.7 mm. or 38.8 per cent greater than the nonrunners. After running, the voltage increased an average of 10.9 per cent. The maximum R + S voltage for the nonrunners was 47 mm. Ten per cent of the tracings taken on the runners at rest exceeded this value (figs. 5 and 6). High voltage persisted for five years after cessation of training in six patients in whom this study was made.

The sum of the height of the R wave in V_1 and the depth of the S wave in V_5 was determined.[10] The average value for the runners at rest was 7.5 mm. (2.0 to 21.0, S.D. 3.3) while after the race it was 9.2 mm. (4.0 to 16.0, S.D. 2.4). Eighteen per cent of the runners' tracings taken at rest revealed amplitudes in excess of 10.5 mm. which is the upper limit of normal given by Sokolow and Friedlander.[10] Forty-two per cent of the runners had values above this after the race.

The sum of the amplitudes of the S waves in V_1 plus the R waves in V_5 ($S_{V_1} + R_{V_5}$) was determined likewise before and after the race. The mean value for the runners' tracings taken at rest was 33.0 mm. (18.0 to 64.0, S.D. 9.0)

TABLE 5.—*Sum of Amplitude of R + S in Lead II. The Maximum Amplitude in the Nonrunners is Exceeded by 15 Per Cent of the Runners at Rest.*

	Nonrunners	Runners	
		Before	After
Mean	13.4	17.2	19.2
Min.	7.0	9.0	10.0
Max.	22.0	40.0	44.0
S.D. ±	3.6	6.5	7.5
C.V. ±%	27.0	37.0	39.0

while after the race it was 35.4 mm. (18.0 to 60.0, S.D. 10.0). Thirty-three per cent of the tracings taken at rest showed amplitudes which exceeded the upper limit of normal given by Sokolow and Friedlander[10] of 35.0 mm., whereas 44 per cent exceeded this value after the race.

The amplitude of the T waves in lead II averaged 2.8 mm. in the nonrunners while the average for the runners at rest was 4.22 mm. or 50.7 per cent greater than the nonrunners (table 7). After running, the T waves increased 14.9 per cent. The maximum T wave was 5.0

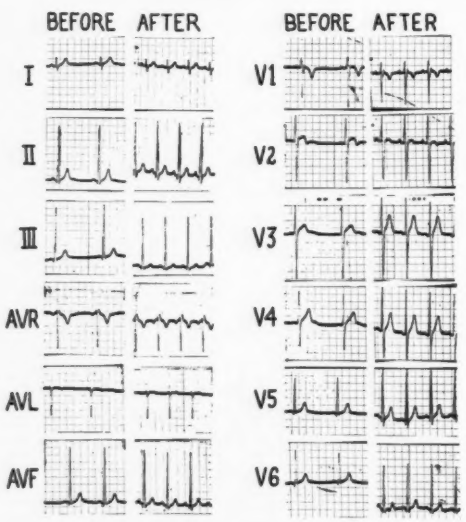


FIG. 6. Electrocardiogram taken before and after race. The vertical position of the heart present before running is unchanged after running. There is high voltage of the QRS complexes which is especially prominent in lead II. Large U waves are seen in V_2, V_3 and V_4. After running there is slight peaking of the P waves and increased cardiac rate with increased amplitude of the T waves in V_3, V_4 and V_5.

TABLE 6.—*Largest R + S Amplitude in Precordial Leads in Nonrunners and Runners. Ten Per Cent of the Runners Had Tracings at Rest which Exceeded the Maximum Value of the Nonrunners.*

	Nonrunners	Runners	
		Before	After
Mean	25.0	34.7	38.5
Min.	15.0	21.0	22.0
Max.	47.0	52.0	58.0
S.D. ±	6.5	8.5	8.5
C.V. ±%	26.0	24.0	22.0

mm. for the nonrunners. Eighteen per cent of the runners' tracings taken at rest showed T waves which exceeded this value.

The height of the tallest T waves in the precordial leads is shown in table 8. In 63 per cent of the runners and in 54 per cent of the nonrunners the tallest T waves occurred in V_3. The average height of the tallest T wave of the precordial leads in the nonrunners was 7.7 mm. as compared with 9.2 mm. in the runners at rest or an average increase of 19.3 per cent. The tallest T wave averaged 12.6 or 36.9 per cent greater after a race than in the tracing taken before the race. The maximum T wave of the precordial leads for the nonrunners was 14 mm.; 16 per cent of the electrocardiograms taken of the runners at rest exceeded this value.

The direction and magnitude of the T wave vectors were calculated for the two groups. The direction of the vector for the nonrunners averaged 38.0 degrees (0 to 76) as compared with 38.4 degrees (0 to 82) for the runners. After a race, these values averaged 45.7 degrees (0 to 87). The magnitude of the T wave axis for the nonrunners was 2.6 units (1 to 5)

TABLE 7.—*Amplitude of T Waves in Lead II Eighteen Per Cent of the Runners' Resting Tracings Exceeded the Upper Limit of Normal of 5.0 mm.*

	Nonrunners	Runners	
		Before	After
Mean	2.8	4.22	4.85
Min.	1.0	2.00	1.00
Max.	5.0	8.00	8.00
S.D. ±	0.85	1.5	1.6
C.V. ±%	30.0	35.0	33.0

TABLE 8.—*Amplitude of Tallest T Waves in Precordial Leads. Sixteen Per Cent of Runners Showed Tracings at Rest which Exceeded the Maximum for the Nonrunners of 14.0.*

	Nonrunners	Runners	
		Before	After
Mean	7.7	9.2	12.6
Min	2.5	2.0	3.0
Max	14.0	17.0	22.0
S.D. ±	2.8	3.6	5.1
C.V. ±%	36.0	38.0	40.0

as compared with 3.6 units (1.2 to 6.5) for the runners before the race. After a race, the value was 3.9 units (2.0 to 6.5). Thus the direction of the T wave axis of the two groups was similar at rest but the magnitude was greater in the runners. After a race, the axis shifted to the right with no significant change in the magnitude. Typical T wave changes after running 26 miles are shown in figure 7.

The S-T segments in the runners were within normal limits before and after running in all subjects except one (fig. 8). This runner had 1.5 mm. negative S-T segment shifts in V_3 and V_4 immediately after running 26 miles. The runner had unusual fatigue but no chest pain. Subsequent tracings showed a return of these segments to the base line in one hour.

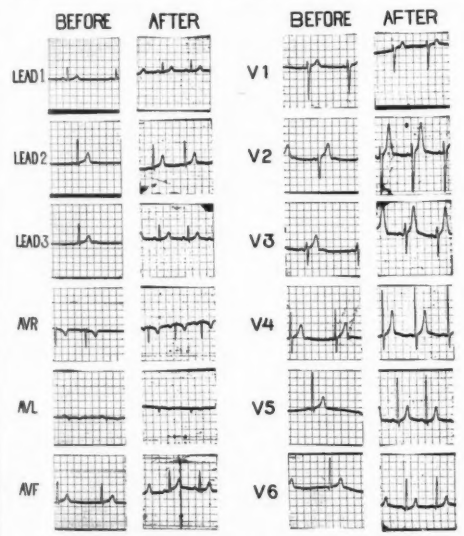


FIG. 7. Electrocardiogram of a marathon runner taken before and five minutes after running 26 miles. The predominant changes are the tall T waves in V_2, V_3 and V_4 after exercise. The height of these waves showed no positive correlation with the blood potassium level.

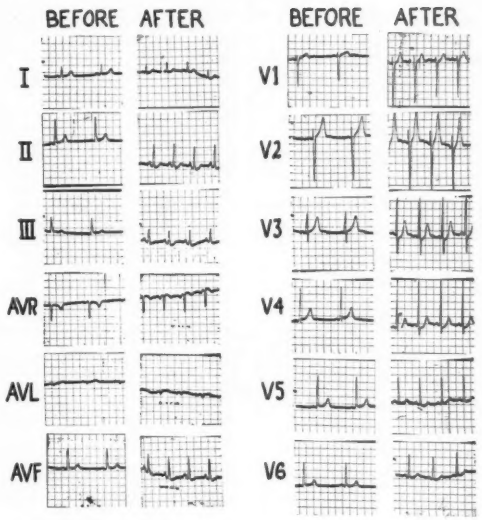


FIG. 8. Negative S-T segment shifts occurred in 1 of the 40 runners after running 26 miles.

The intrinsicoid deflection was measured in tracings made with the string galvanometer on 20 nonrunners at rest and on 20 runners. In lead V_1 the nonrunners showed a mean time of 0.014 second (0.005 to 0.030, S.D. 0.003) compared with the runners whose resting tracings showed values of 0.030 (0.020 to 0.050, S.D. 0.003). After the race the runners had values of 0.031 second (0.020 to 0.050, S.D. 0.008). In V_6 the nonrunners showed an average of 0.038 second (0.020 to 0.050, S.D. 0.005) compared with the tracings of the runners taken at rest of 0.049 second (0.040 to 0.060, S.D. 0.008). Thus the intrinsicoid deflection time was longer in the runners in V_1 and in V_6 than in the nonrunners.

The corrected Q-T interval (Q-Tc) was measured in both groups: The mean value before running was 0.40 second (0.33 to 0.45, S.D. 0.044). After running the value was 0.41 second (0.36 to 0.47, S.D. 0.036). The nonrunners averaged 0.40 second (0.35 to 0.45). Thus the Q-T interval was not abnormal before or after running.

TABLE 9.—*Transverse, Broad, Long and Great Vessel Diameters as well as Cardiac Areas in 40 Runners and Nonrunners*

	Transverse		Broad		Long		Area		Great Vessel Diameter	
	Non runners	Runners	Non runners	Runners	Non runners	Runners	Non runners	Runners	Non runners	Runners
Mean	121	129	112	117	139	150	123	139	51	5
Min.	104	106	110	105	130	136	112	113	42	4
Max.	139	143	115	132	148	175	136	182	57	6
S. D. ±	12	12	0.8	6	6.6	4.8	6.9	14	3.6	4.
C. V. ±%	10	9	0.7	5	4.7	3.2	5.6	10	7.0	8.

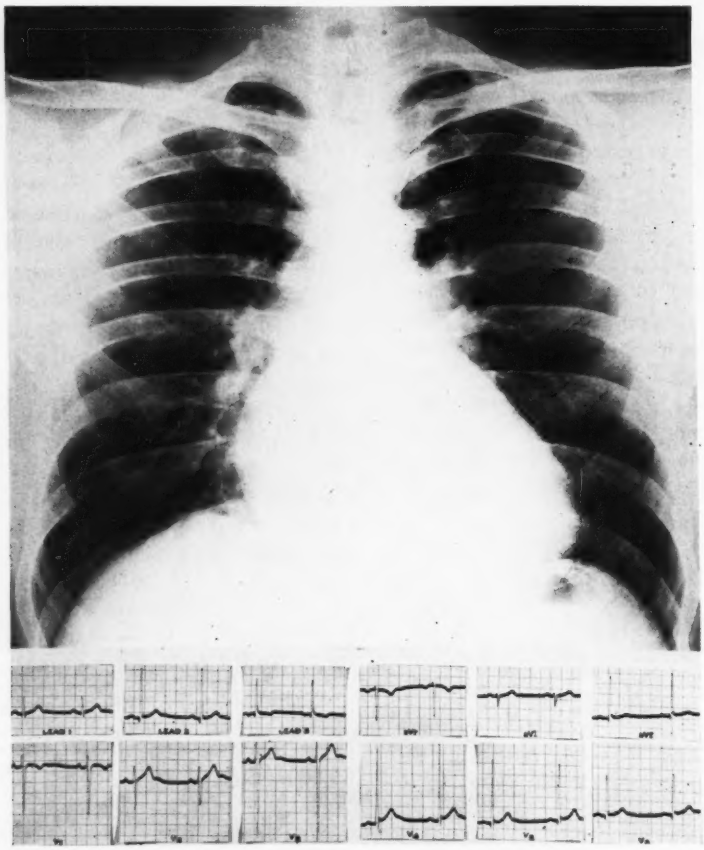


FIG. 9. Teleoroentgenogram and electrocardiogram of a 45 year old runner who has trained for 20 years. The cardiac area, as well as the long, transverse and broad diameters exceed normal values for his height and weight. High voltage of QRS complexes is a prominent feature of the electrocardiogram. The S waves in V_3 are deep.

The ventricular gradient was calculated for both groups. The direction for the nonrunners averaged 53 degrees (2 to 89) and for the runners at rest 61 degrees (0 to 84). After running the average was 66 degrees (7 to 87). The magnitude for the nonrunners averaged 11.3 units (4.4 to 17.8) as compared with the runners at rest which averaged 17.4 units

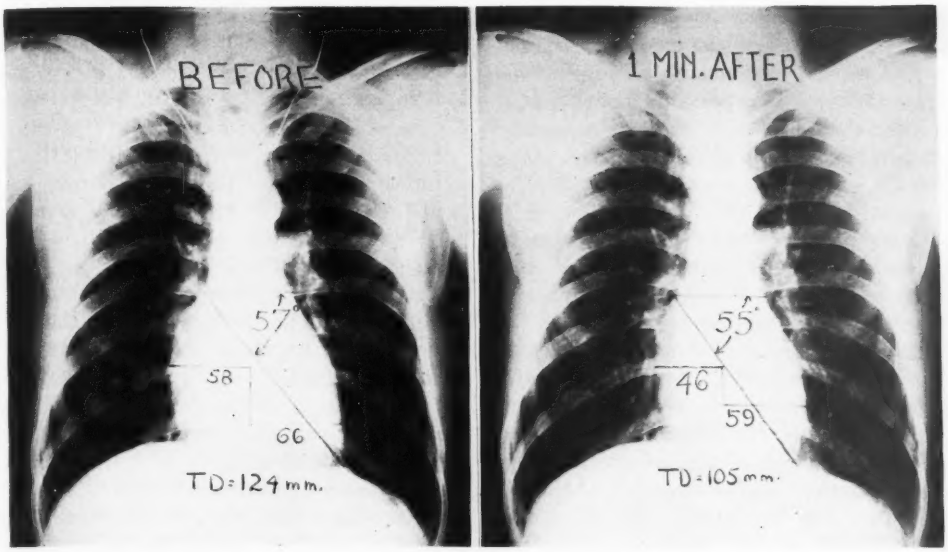


FIG. 10. Cardiac shadow of a runner before and after running 26 miles. The cardiac shadow is small after running compared with the resting size.

(10.3 to 45.8). After running the magnitude averaged 18.6 units (9.8 to 43.2). Thus in the runners the gradient vector was slightly more to the right than in the nonrunners and the magnitude of the gradient averaged 53.9 per cent greater in the runners at rest than in the nonrunners.

The positional relationships between the QRS, G, T and H axes were calculated for both groups. The anatomic axis (H) for nonrunners averaged 42 degrees (28.0 to 59.0) as compared with that for the runners, which was slightly more vertical averaging 44 degrees (32.0 to 57.0). A comparison of the various vectors with each other showed that among the runners: (1) the T axis was to the left (negative) of the QRS axis by an average of 29 degrees while the average for the nonrunners was 26 degrees to the left; (2) the average QRS axis was to the right of the average gradient by 6 degrees as compared with 5 degrees for the nonrunners; (3) the average magnitude of the gradient was longer than the magnitude of the QRS complex by 3 units as compared with 2.4 units for the nonrunners, and (4) the average gradient was to the right (plus) of H by 17 degrees, the average for nonrunners being 19 degrees. These findings may be interpreted as indicating that the QRS complexes and T waves are in normal relationship to each other and are likewise in normal relationship to the anatomic position of the heart in the chest.

Teleoroentgenographic Findings. The cardiac size was measured from posteroanterior teleoroentgenograms in both groups (table 9). The transverse measurements of the runners averaged 6.6 per cent greater than the controls. Likewise the actual transverse measurements of the runners exceeded the predicted values by 5.8 per cent. The prediction was based on the height and weight according to the method of Ungerleider and Gubner.[9] The average broad measurements of the heart of the runners exceeded the average of the nonrunners by 4.5 per cent. The average long measurements of the runners exceeded that of the nonrunners by 7.9 per cent. The average cardiac area of the runners exceeded that of the nonrunners by 13.0 per cent and the runners showed a 15.8 per cent increase over that predicted from their height and weight.[7] The average great vessel diameter of the runners exceeded the normal by 5.8 per cent. A typical teleoroentgenogram of a 45 year old veteran runner taken with the subject at rest is shown in figure 9.

The cardiac size in 10 subjects was com-

pared before and after they had run 26 miles. Five of these had teleoroentgenograms and five had x-ray kymograms. In all subjects the cardiac shadow was considerably smaller after the race than before. A typical example is shown in figure 10.

Discussion

The cardiovascular adaptations to prolonged physical training are as follows: The electrocardiograms taken with the runners at rest show definite changes which fall outside the generally accepted limits of normal as well as outside the values seen in the nonrunners who served as controls. The P waves of the electrocardiograms taken on the runners at rest were of normal size and configuration and their electric axes were shifted slightly to the right. The duration of the QRS complexes at rest was increased, which is in keeping with the findings of others. The intrinsicoid deflection times were prolonged in V_1 and V_6, which suggests hypertrophy of the right and left ventricles. High voltage of the QRS complexes in the standard and precordial leads was exceedingly common, which indicates also ventricular hypertrophy. This appears to be a physiologic adaptation to intensive prolonged physical training of the endurance type and is not a sign of disease as suggested by normal ventricular gradients in all cases. The increased voltage of QRS often was present in both standard and precordial leads, indicating that the etiology was related to the heart and that the voltage was not due to the position of the heart in the chest. In general the electrocardiographic position was semivertical and the electric axis of the QRS complex was shifted slightly to the right. The ventricular gradient was well within normal limits indicating that the relationship of QRS to T was within normal limits. The U waves were large and superimposed often on the downstroke of the T wave. These waves were in keeping with cardiac enlargement. The ventricular gradient was shifted slightly to the right which is in keeping with the somewhat more vertical position of the heart of the runners than of the controls. The high voltage of QRS and of the T waves and more vertical position of the heart has been described by others.[11-13] The sum of the amplitude of S_{V_1} and R_{V_5} normally does not exceed 35 mm. and an increase over this has been advocated as a sign of left ventricular enlargement.[10] By this guide left ventricular enlargement occurred in 33 per cent of the runners. The sum of R_{V_1} and S_{V_5} normally does not exceed 10.5[10]; however, this value was exceeded in 18 per cent of the runners. This suggests right ventricular enlargement. The resting cardiac rate was slower generally in the runners than in the nonrunners. The entire electrocardiographic picture of slow rate, high voltage of QRS, T and U, ventricular gradient of increased magnitude and normal relationships of the electric axes to each other is characteristic of the athlete who has had prolonged, intensive training. This picture remains present for at least five years after training has ceased. In 3 of 40 runners an R-R prime wave was found in lead V_1 which remained for at least five years. It seems probable that this resulted from right ventricular strain and may represent a harmful effect of endurance running.

The acute cardiovascular adaptations to prolonged physical effort as seen in this series are based on findings seen immediately after running 26 miles and are as follows: The P waves increased in amplitude and duration in lead II in our series and in the studies of others[14, 15] and rightward deviation of the P-wave axis took place.[16] These changes were not the result of the inspiratory position of the diaphragm or the increased volume of air in the lungs, as waves of this type could not be produced in the nonrunners by holding the breath in the inspiratory position. The auricular T waves were exceptionally large and were opposite in direction to the P waves in those runners whose P waves were exceptionally large. The P-R interval decreased in all cases except one in which it was increased. An increase such as this after exercise compared with the resting is said to be indicative of disease.[17] In the runners, however, the absolute value of 0.22 second was not exceeded; thus it is not certain that this is due to disease.[18-20] The duration of the QRS complexes decreased in all cases after exercise. This is a normal re-

sponse to exercise.[21] The voltage of the QRS complexes increased fairly consistently after exercise, and this is usual after prolonged exercise.[14] Again this degree of increased voltage could not be duplicated by the nonrunners by holding the breath in inspiration. This suggests that the cause of the high voltage was cardiac rather than extracardiac. The electric axis of QRS complexes deviated to the right after exercise.[11] The RS-T segments measured from the P-R level just before the QRS complexes exceeded the limit of normal in one runner.[22] This subject appeared disorientated and unusually exhausted after running but had no chest pain. The infrequency of this finding suggests that this is a pathologic response to exercise. The T-waves showed large increases in amplitude after severe exercise, which is in keeping with the findings of others.[23, 24] The changes were greatest in the leads with the tallest QRS complexes. This increase in the voltage of T was the most conspicuous result of exercise in many cases. The changes in the blood potassium did not explain these changes. These waves were not accompanied by abnormal gradients, and thus were not considered to be the result of ischemia. Others have reported inverted T waves in leads II and V_4, V_5, and V_6 with intensive exercise but this was not noted in this series.[25] The T axis moved to the right.[16] The Q-Tc interval changed little as a result of running. In one case the Q-Tc exceeded the upper limit of normal of 0.45 second. In no other instance was the degree of prolongation of Q-Tc comparable to that seen in patients with heart disease after exercise.[26]

Teleoroentgenograms of the hearts of the runners at rest showed the presence of cardiac enlargement in a significant percentage of subjects. The greatest increase above normal of the cardiac measurements was in the cardiac area. Both the long and broad diameters of the heart were increased likewise above normal. In general the x-ray films revealed a cardiac silhouette which was long and extended to the left. The pulmonary artery and pulmonary vascular markings were considerably increased in diameter and density. The great vessel shadows were large. Immediately after running 26 miles the cardiac shadow was considerably smaller.

Summary

The electrocardiographic, radiologic, electrolytic and other findings are described in 165, 26-mile marathon runners and 40 normal control nonrunners. There was a characteristic electrocardiographic picture which consisted of a slow cardiac rate with high voltage of QRS complexes, T and U waves. The picture is characteristic of right and left ventricular enlargement without evidence of cardiac disease. Radiologically the heart was enlarged in its broad, long and transverse diameters before the race and was considerably smaller immediately after running. The recognition of this picture and its relation to previous physical training is important in the differential diagnosis of cardiac enlargement.

Acknowledgments

Gratitude is expressed to Mrs. Jean Schnear for the statistical analysis, and to Mrs. Cora Lord for technical assistance.

Sumario Español

Los hallazgos electrocardiográficos, radiológicos, electrolíticos y otros se describen en 165 corredores del maratón de 26 millas y en 40 controles normales no corredores. Se encontró un cuadro electrocardiográfico característico que consistió de un pulso bajo con alto voltaje de los complejos QRS y las ondas T y U. El cuadro es característico de engrandecimiento ventricular derecho e izquierdo sin evidencia de enfermedad cardíaca. Radiologicamente el corazón se encontró engrandecido en su diámetro ancho, transverso y largo antes de la carrera y considerablemente más pequeño luego de la carrera. El reconocimiento de este cuadro y su relación a previo entrenamiento físico es importante en el diagnóstico diferencial de engrandecimiento cardíaco.

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Circulatory Changes in Acute Myocardial Infarction

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Using the dye dilution technic of Hamilton the cardiac output was measured in 20 patients with acute myocardial infarction. The blood pressure, circulation time, venous pressure, plasma volume, and hematocrit were also determined. Those patients who developed congestive heart failure had a low cardiac output and a prolonged circulation time. These changes were more pronounced in seven patients with sustained shock. One patient who had just recovered from circulatory collapse was found to have a cardiac output of 9.3 liters per minute.

IT IS well known that congestive heart failure and collapse after an acute myocardial infarction diminish the chances for survival. Yet our understanding of the accompanying circulatory changes has been meager because of the hazards of carrying out complicated studies in such seriously ill patients.

With the introduction of a reliable and safe technic for measuring the cardiac output without moving the patient,[1-3] it has become possible to make such determinations at the bedside. The present report concerns our results in 20 patients with recent acute myocardial infarction. Thirteen of these patients manifested congestive heart failure or shock, while the remaining seven patients were in no obvious circulatory embarrassment. The cardiac output was determined by the dye dilution technic of Hamilton.[1] The following measurements were also made: circulation time, peripheral venous pressure, arterial pressure, hematocrit, and Evans blue plasma volume. It is hoped that such information will not only enlighten our understanding of the circulatory defects resulting from acute myocardial infarction but will assist in planning effective treatment.

No attempt will be made to review the reports of animal experiments. These experiments have been cited elsewhere.[4-6] In general they have shown a lowering of the cardiac output without a corresponding drop in arterial pressure. Clinical reports of individual cases have confirmed this in the main.[7-10] Data obtained by the ballistocardiograph[11] and by pressure-pulse measurements[12, 13] have also indicated lowering of the cardiac output. Recent studies in this laboratory and elsewhere have shown a reduction of the cardiac index after acute myocardial infarction which is more marked in patients with shock.[14-16]

MATERIAL

Successful determinations were completed in 19 male patients and 1 female patient, aged 33 to 78 years. In all cases the clinical diagnosis of an acute myocardial infarction was confirmed by unequivocal electrocardiographic changes. In all but one case the actual infarction had occurred 6 to 48 hours prior to study, as judged from the history. In this one instance the infarction had apparently happened four days previously, although shock had been present only six hours. The diagnosis of congestive heart failure was based solely on the clinical findings, chiefly, the presence of dyspnea, basal rales, and sometimes venous distention and hepatomegaly. Patients were considered to be in a shock-like condition when they manifested weakness, sweating, a cloudy mental state, thready or impalpable radial pulse, and cold extremities. Severe hypotension was present in two cases. The degree of failure or shock was roughly estimated on a 0 to 4 plus scale and is indicated in table 1 along with the age, sex, and probable time interval after infarction.

METHODS AND PROCEDURE

The cardiac output was determined with Evans blue dye (T-1824) by the method of Hamilton.[1] Collection times were signalled on an electrocardiograph camera which also served to record arterial pressure from a strain gauge manometer.

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TABLE 1.—*Results in Twenty Cases Ranked by Cardiac Index*

Case§	Age	Hours after onset	Failure	Shock	Outcome	Cardiac Index L./min./M.²	Cardiac output L./min.	Femoral B.P. mm. Hg.	Mean B.P. mm. Hg	Circ. Time sec.	Venous Pressure mm. H_2O	Rate	TPR dyne sec. $cm.^{-5}$	Plasma Volume ml./Kg.	Hematocrit
1. LD	53	30	0	0	L	3.3	6.0	133/77	101	15	140	107	1300	28	38
2. MA	67	13	0	0	L	3.2	5.2	168/71	108	16	75	82	1600	40	41
3. AU	61	14	0	0	L	3.1	5.7	163/74	107	20	178	105	1400	41	39
4. RH	66	48	0	0	L	2.5	4.3	124/63	85	23	120	69	1500	40	42
5. BR	62	24	0	0	D	2.4	4.5	148/93	118	25	235	96	1900	27	35
6. DU	72	12	+	0	D	2.2	3.8	111/62	86	32*	245	120	1600	31	37
7. FE	50	19	0	0	L	2.1	3.9	129/72	91	25	94	73	1750	40	46
8. PO	42	9	2+	0	D	2.1	3.7	117/82	94	28	188	105	1900	38	43
9. SK	62	8	3+	0	L†	2.0	3.9	170/98	122	25	210	93	2300	29	33
10. ZA	63	48	±	0	D	1.8	3.1	117/77	91	13	190	101	2100	22	36
11. CA		24	+	0	D	1.8	3.3	135/74	98	28	60	109	2300	51	46
12. OH	61	24	0	0	L	1.7	3.1	118/68	91	15	78	94	2300	25	47
13. PA	59	8	+	0	D	1.5	2.4	141/88	111	33*	110	105	3600	33	46
14. HE	33	18	2+	+	D	1.4	2.6	124/88	100	38	374	133	3000	29	35
15. MA	50	46	+	+	D	1.2	2.1	102/90‡	96‡	40	270		3200	59	39
16. RO	64	96	+	+	D	1.1	2.2	114/57	70	30	223	51	2300		46
17. HA	52	6	3+	2+	D	1.1	1.9	111/67	87	45	179	77	3300	35	54
18. WO	78	49	+	3+	D	0.8	1.5	102/52	81	42	220	114	3900	35	47
19. GR	75	16	+	3+	D	0.8	1.2	65/43	54	60	65	88	3400	47	44
20. LO	78	6	+	4+	D	0.6	0.9	45/18	25	77	175	53	1600		44
Averages						1.8	3.3		91	32	171	93	2300	36	47
S.D.						0.8	1.6		22	16	80	22	800	9	5

* Circulation time from peak of dye curve. † Patient left hospital against advice on tenth day. ‡ Blood pressures by auscultatory method. § All patients males except 20.LO.

In order to estimate the appropriate rate of arterial sampling, the arm-to-tongue circulation time was first measured with Decholin through a calibrated needle in the antecubital vein. This needle was kept open by periodic flushing from the venous pressure manometer and was used later for the dye injection. A 15 or 17 gauge needle was inserted in the femoral artery after procainization. A three-way stopcock connected this needle to the strain gauge or to a curved metal tube for delivering blood samples. Two ml. of 0.5 per cent Evans blue dye (T-1824) were injected from a calibrated 2 ml. tuberculin type syringe. Arterial samples were then collected at 2 to 5 second intervals with a straight rack of tubes containing heparin powder. A single 10-minute sample was taken for estimation of the plasma volume. The plasma dye concentrations were read in the Evelyn photoelectric microcolorimeter. Hematocrits were measured in duplicate in Wintrobe tubes spun for 30 minutes at 3500 revolutions per minute at a 15-cm. radius (axis to tube tip).

Surface area was estimated by nomogram from the height and weight values furnished by the patient. Mean arterial pressures were measured either by planimeter or by averaging pressure values read from the tracing at 0.04 second intervals. The total peripheral resistance was calculated by the formula[17]:

$$\textit{Total peripheral resistance} = \frac{(\textit{Mean arterial pressure} - \tfrac{1}{2}\ \textit{venous pressure}) \times 1332}{\textit{cc. of cardiac output/second}} \quad (17)$$

The peripheral venous pressure was halved to approximate the right atrial pressure,[16] though it was recognized that the pressure gradient may be diminished in congestive failure.[18]

RESULTS

The results are ranged in table 1 in order of descending cardiac index. It is evident that with decreasing values for the cardiac index, the following changes occur: (1) increasing mortality rate, (2) appearance of failure and then shock, (3) increasing circulation time, and (4) usually increasing total peripheral resistance. The average cardiac index for all cases was 1.8 ± 0.8 liters per minute per square meter of body surface area. The mean venous pressure was elevated and the average circulation time prolonged.

In figure 1 the mean femoral arterial pressures are plotted against the corresponding

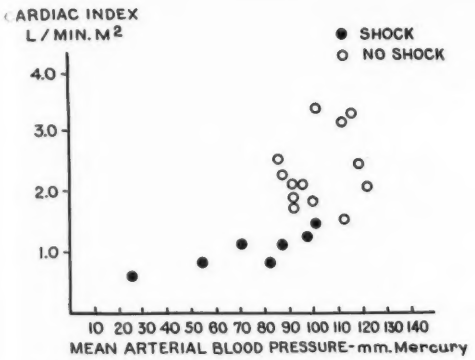

FIG. 1. Cardiac index (liters/min./M.²) and mean femoral arterial pressure in 20 patients with acute myocardial infarction.

cardiac indices. The arterial pressures are seen to lie within the normal range despite low indices except in three patients with extreme lowering of the cardiac index. Accordingly, the calculated values for the total peripheral resistance are increased in most instances. Figure 2 illustrates the expected lengthening of the Decholin circulation time in patients with low cardiac indices ($r = -.765$, $p < .01$). The patients who survived had shorter circulation times. No correlation was found between the cardiac index and the venous pressure ($r = -.20$, $p > .40$). The venous pressure was elevated in two patients without clinically apparent heart failure and was normal in three patients with obvious cardiac insufficiency. Pressure on the right upper

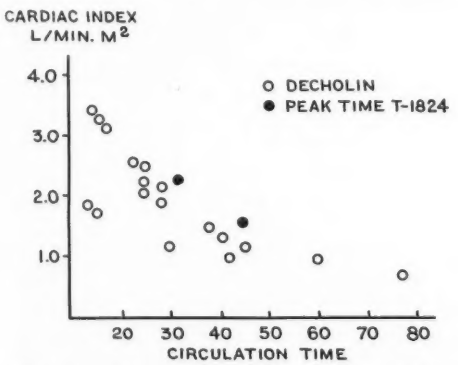

FIG. 2. Cardiac index (liters/min./M.²) and circulation time in 20 patients with acute myocardial infarction.

TABLE 2.—*Average Figures for the Three Groups*

Group	No. Pts.	Cardiac Index L/min./M.²	Circ. Time sec.	Venous Pressure mm. H_2O	Hematocrit	Plasma Volume ml./Kg.
Group I						
No fail.	7	2.61	19.9	130	45.	34.4
No shock						
2·S.E.		.46	3.4	44.3	2.3	5.6
Group II						
Failure	6	1.9	24.8	167	50.	34.1
2·S.E.		.20	5.41	56.2	4.8	8.2
Group III						
Shock	7	1.0	47.4	215	47.1	40.0
2·S.E.		.21	12.	83.4	4.4	7.9

quadrant of the abdomen caused the venous pressure to rise in some patients without signs of failure and usually produced a rise in those with obvious failure.

Three subgroups are compared in table 2. The first group comprises those patients with no *clinical* evidence of either failure or shock. Those in the second group showed signs of heart failure. The cases in the third group were in a shock-like condition, and all had signs of congestive failure. In addition to significantly lower cardiac indices in the patients with failure and shock, the circulation times are also seen to be lengthened. No differences are apparent for the average hematocrits or plasma volumes, and the differences in mean venous pressure values are not significant because of the large deviations

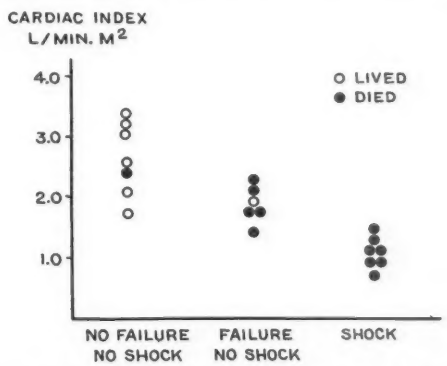

FIG. 3. Comparison of cardiac index (liters/min./M.²) in three subgroups. Presence of failure or shock determined on clinical grounds. Other data in table 2.

from the mean. The cardiac indexes for these three groups are portrayed in figure 3. While there is some overlapping, the cardiac index is usually lower when there is heart failure and still lower in shock. The open circles indicate patients who survived the hospitalization period, usually those patients who had fairly normal outputs. The strikingly high mortality rate can be explained by the fact that there was a tendency to select for study those patients who were more seriously affected.

The individual findings in shock are shown in more detail by the last seven cases in table 1, which can be compared with the average values given in table 2. While the femoral arterial pressures were severely depressed in only two cases, the auscultatory pressures obtained in the arm were often lower than those obtained by direct recording from the femoral artery. In other respects these patients showed the clinical picture of shock described above, and differed from each other only quantitatively. Three patients with normal pressure had histories of hypertension. All had been in a shock-like condition for at least six hours prior to study. Only the first of the patients with shock survived longer than 12 hours. The third patient was studied four days after the onset of pain, five to six hours after going into shock. They all were dyspneic and most had rales. The extreme reduction of their cardiac indices may have been exaggerated by the hidden recirculation error, particularly in the second, fourth and sixth cases. Curves in these cases had overly rounded peaks and slow downslopes. However in one case which was not included in the table because the data were incomplete, the cardiac output was 9.3 liters per minute and the blood pressure 138/78 some 12 hours after recovery from circulatory collapse. On admission the blood pressure was unobtainable. No pressor therapy was used.

The circulation time in the shock group was uniformly prolonged, and the venous pressure was normal in only one instance. The hematocrits were not remarkable. The plasma volume was not found to be especially low in those patients with shock despite the fact that slow mixing in such cases might be expected to give higher dye concentrations at ten minutes. Despite the presence of shock and low cardiac indices, two cases showed no increase in heart rate. Auriculoventricular block accounted for the slow rates in cases 16 and 20.

Discussion

These results agree with those reported by Freis[15] and Smith[16] and described less completely by others.[7-13] Following acute myocardial infarction the cardiac index is usually low. The degree of reduction is roughly proportional to the clinical severity of the attack and is most marked in patients with sustained shock. The relationship is by no means an absolute one, as exemplified by patient 12, who appeared to be in good condition in spite of a cardiac index of only 1.7. Smith reported two similar cases.[16] Except in those cases with very low cardiac indexes the blood pressure tends to be well sustained, indicating overall vasoconstriction. There is no significant correlation between a high venous pressure and a low cardiac index, nor between a high venous pressure and a long circulation time. The longer circulation times were associated with lower cardiac indices. Quite possibly this association accounts for the usefulness of the circulation time as a guide to the severity of myocardial infarction. The patients with shock were not found to have particularly low plasma volumes, contrary to the data shown by Agress and co-workers[19] and hinted at by others.[5, 20] Resolution of this question awaits a more precise method for determining *plasma* volumes. It is quite possible that the lower plasma volume found in some cases is the result not only of dehydration but of a high venous pressure. We found no significant correlation between the venous pressure and the plasma volume ($r = -.259$, $p > .30$) but there was a correlation coefficient of 0.40 ($p < .10 > .05$) between the venous pressure and the hematocrit and a significant correlation between high hematocrit and low plasma volume ($r = -.653$, $p < .01$). In two cases followed serially the hematocrit dropped from 55 to 44, and from 44 to 39 in several days, while the venous pressure changed from 384 to 215 and from 205 to 210 mm. saline.

The genesis of shock in acute myocardial infarction cannot yet be precisely described

from the data at hand. Harrison,[21] Stead,[22] Boyer,[5] and others have held that it results from inability of the heart to deliver enough blood despite a more than adequate venous supply. This view is strongly supported by our data and that of others.[15, 16] Various workers[4, 20, 23] have suggested that shock after infarction may also result from peripheral vasodilatation. The one patient with a cardiac output of 9.3 liters per minute after recovery from circulatory collapse could represent such an occurrence. So could the one with a cardiac output of 5.3 liters per minute and a blood pressure of 66/44 reported by Stead.[24] One of Freis' patients was in shock despite a cardiac index of 2.4.[15] It is quite possible that some of the patients who were found to have a low cardiac output several hours after the onset of shock had a considerably higher output at the beginning. Prolonged hypotension is well known to seriously affect the myocardium of previously normal animals,[25] not to mention the hearts of patients with generalized coronary artery disease.[26] It is likely that many patients who recover spontaneously from *brief* periods of collapse shortly after the onset of infarction would be found to have a normal or even elevated cardiac output at the time of collapse.[23] We have no data from such cases. It does not seem likely that there is enough reduction of plasma volume to contribute significantly to shock. While both central and peripheral factors may operate initially to produce shock in acute myocardial infarction, it seems clear that in sustained shock there is a low output because of a failing heart.

Insofar as reduction in the cardiac index is the chief circulatory defect in sustained shock due to acute myocardial infarction, it seems logical that the output should be supported as well as possible. The obvious drugs for this purpose are the digitalis glycosides[9] and the xanthines. Aminophylline in acute myocardial infarction seems to have such an effect.[27] Measures to restore aortic pressure might increase the cardiac output by improving coronary perfusion of uninvolved and marginally infarcted areas.[28] Some of the reports concerning pressor agents and infusions[29, 30] are encouraging. Elucidation of this problem requires more objective data concerning the dynamic effects of such measures in myocardial infarction.

Summary

1. Cardiac index, blood pressure, venous pressure, circulation time, plasma volume, and hematocrit were determined in 20 patients soon after acute myocardial infarction.

2. Lowering of the cardiac index and prolongation of the circulation time were roughly proportional to the clinical severity of the attack.

3. Vasoconstriction tended to sustain the blood pressure as evidenced by increased values for the peripheral resistance.

4. In patients with sustained shock the cardiac index was particularly low, though no major plasma volume changes were evident in this group. One patient who had recovered from profound circulatory collapse was found to have a cardiac output of 9.3 liters per minute.

5. The possibility of normal or high output at the onset of shock is discussed.

Acknowledgments

The authors gratefully acknowledge the work of Stephen Aldrich, M.D. and Lynn Anderson, M.D. who participated in the early phases of this project.

Sumario Español

1. En 20 pacientes con infarto del miocardio reciente se determinó el índice cardíaco, la presión arterial, presión venosa, tiempo de circulación, volumen plasmático y hematocrito.

2. Decremento del índice cardíaco y prolongación del tiempo de circulación fueron aproximadamente proporcionales a la severidad clínica del ataque.

3. La vasoconstricción tendió a sostener la presión arterial como fué comprobado por los valores aumentados en resistencia periférica.

4. En pacientes en choque sostenido el índice cardíaco fué particularmente bajo, aunque cambios significativos en el volumen plasmático no fueron evidentes en este grupo. Un paciente que había recobrado de un colapso circulatorio profundo se encontró tener una producción cardíaca de 9.13 litros por minuto.

5. La posibilidad de producción normal o alta al comienzo del choque se discute.

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Stokes-Adams Attacks with Simultaneous Auricular and Ventricular Standstill

By NAIP TUNA, M.D. AND JOHN W. SCOTT, M.D.

This is a report of a case of Stokes-Adams seizures in a patient with partial auriculoventricular block. Simultaneous auricular and ventricular standstill in about half the seizures of which we have electrocardiographic record, and complete relief after atropine, leads us to think the seizures were due to vagal effect.

SINCE it was first described in the literature,[1, 2, 3] much has been written about the Stokes-Adams syndrome. The ventricular mechanism and the changes in auriculoventricular conduction have been investigated extensively. The usual mechanism of these attacks is prolonged ventricular asystole, or ventricular tachycardia, flutter or fibrillation of long duration.[4]

Many observers have described similar attacks resulting from reflexes arising from the carotid sinus or from other sources, such as Brandenburger's three patients with Mikulicz's syndrome,[5] Gluck's case of neoplasm of a bronchus causing pressure on the vagus,[6] Flaum and Klima's case of acute tonsillitis,[7] Weiss and Ferris's patient with esophageal diverticulum[8] and Scott and Sancetta's patient with Stokes-Adams syndrome who had these attacks when straining at stool or from digital irritation of the anal sphincter.[9] In most of these instances there was total cardiac standstill during the attack without underlying heart block.

Such attacks have been termed the "neurogenic" Stokes-Adams syndrome.[10] Many have considered them as merely syncope and not true Stokes-Adams attacks. Although lesions of the myocardium or temporary ischemia may have a definite influence upon the occurrence of such attacks, an additional neurogenic factor such as vagal stimulation may play an important role in their production.[11] This factor seems not to have been emphasized sufficiently. The case to be reported shows the additive effect of vagal stimulation in the production of such an attack in a patient with arteriosclerotic heart disease and auriculoventricular and intraventricular block.

From the Medical Service of St. Joseph Hospital, Lexington, Ky.

CASE REPORT

A 75 year old white man was admitted to the hospital on May 14, 1953, complaining of attacks of unconsciousness of two or three minutes duration. For periods of approximately 20 seconds the patient's son, a physician, was unable to feel the pulse during these attacks. For three months he had as many as 20 to 50 attacks each day.

For 15 years he had had dizzy spells during sudden movement, for seven years dyspnea on exertion and in nocturnal paroxyms and for four years known hypertension. The family history was not significant. He was well developed and fairly well nourished. The blood pressure was 165/90; the pulse was 76 per minute. The palpable arteries were tortuous and sclerotic; the ocular fundi showed moderate arteriosclerosis. The heart was not enlarged and the rhythm was regular. There was a harsh systolic murmur of moderate intensity at the apex and a blowing systolic murmur at the aortic area. The prostate showed moderate benign hypertrophy. There were no other significant abnormalities.

Urinalysis was negative. The blood count showed erythrocytes 3,500,000, hemoglobin 9 Gm., leukocytes 8,000 with normal differential count. The erythrocyte sedimentation rate was 17 mm. in one hour (Cutler). Roentgenogram of the chest showed no cardiac enlargement. The electrocardiogram on admission (fig. 1 *A*) showed first degree A-V heart block and right bundle branch block; the duration of the P-R interval was 0.28 second, of the QRS complex 0.14 second. There was regular sinus mechanism and the rate was 64 per minute.

Shortly after admission seizures of two kinds began to occur; these recurred every 5 or 10 minutes. In the milder ones there were generalized muscular twitchings and flushing of the face, without impairment of consciousness. In the more severe seizures there was loss of consciousness with generalized clonic convulsions. Serial electrocardiograms were obtained. In addition to bundle branch block these

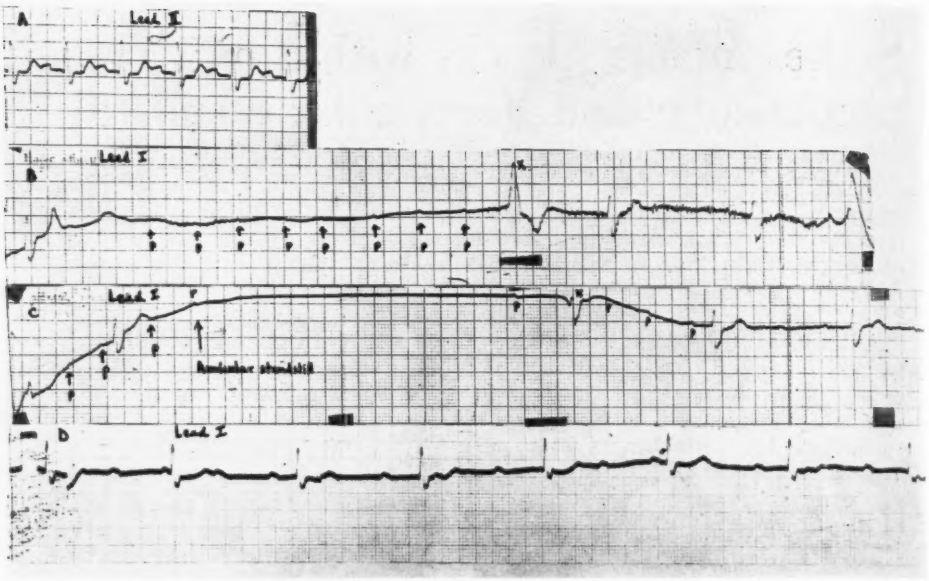

FIG. 1. (*A*) Record on admission: First degree auriculoventricular block and right bundle branch block. P-R interval 0.28 second, duration of QRS 0.14 second. (*B*) Record during attack: Ventricular asystole with normal auricular mechanism (rate increased). Auricular systoles are marked (p). Mechanism resumed with ectopic beat (x). (*C*) Record during attack: Auricular and ventricular asystole preceded by ventricular complexes. (*D*) Record four months later: Complete auriculoventricular block; duration of QRS 0.12 second.

records showed two types of conduction disturbance: (1) A-V block with ventricular asystole, the auricular rate increasing from 93 to 110 per minute during the asystole (fig. 1 *B*), and (2) simultaneous auricular and ventricular asystole (fig. 1 *C*). The latter occurred in about half the major attacks of which we have record. Loss of consciousness occurred when the ventricular asystole was prolonged. Immediately after the attacks the auricular rate returned to its initial level.

The duration of the longest ventricular asystole with normal auricular mechanism was six seconds. When auricular asystole was also present the longest duration was 5.6 seconds. Each auricular standstill was preceded by two or three ventricular complexes of incomplete 2:1 or 3:1 A-V block; in no instance did it follow ventricular asystole of longer duration. Except for these two or three cycles of high grade block, the basic mechanism preceding auricular asystole was first degree A-V block with long P-R intervals.

On the day of admission he had attacks every 5 or 10 minutes. Ephedrine sulfate was given in 25 mg. doses every three hours without benefit. (It was learned later that the drug had been used previously without effect.) Because of A-V block and frequent auricular standstill it occurred to us that vagal stimulation might be the cause of the attacks. Accordingly, atropine sulfate, 0.9 mg., every six hours, was ordered. The attacks ceased before the second dose was given and did not recur before he left the hospital 60 hours later. Urinary retention developed the second day after atropine was begun.

After leaving the hospital he was not under our observation. It was reported that he had used varying amounts of atropine. The attacks were relieved when the doses were sufficiently large and recurred on smaller doses. Six weeks after discharge from the hospital suprapubic cystostomy was done elsewhere. Following this he is said to have had atropine sulfate, 0.9 mg. three times daily, with complete relief from seizures.

On September 25, when he was seen last, it was found that he had gradually reduced the atropine to 0.9 mg. once daily and had experienced no seizure between June 27 and that date. At that time an electrocardiogram showed complete A-V block (fig. 1 *D*).

DISCUSSION

In the case reported here ventricular standstill was the cause of Stokes-Adams attacks. The auricular rate increased during ventricular standstill, as reported in similar cases.[12-15] In our case, in approximately half of the

seizures of which we have electrocardiographic record, standstill of auricles and ventricles occurred simultaneously. Heretofore, 20 seconds has been the shortest recorded duration of ventricular standstill producing auricular asystole.[4] Shorter duration of ventricular standstill is usually followed by acceleration of the auricular rate. For this reason it would seem that auricular asystole occurring, as it did in our case, without the asphyctic effect of prolonged ventricular standstill, must be explained by vagal effect. This hypothesis is supported by the fact that before each episode of complete asystole there was a brief period of 2:1 or 3:1 A-V block. The idea is supported further by relief of the seizures by atropine. It is thought that our case should not be included among the rare instances of Stokes-Adams attacks in which atropine has been effective by unexplained mechanism.[16]

It is notable that during the several months of our observation the electrocardiogram has changed to permanent complete auriculoventricular block. It seems likely that the development of an idioventricular mechanism has stabilized the rhythm and is a factor in freedom from attacks on smaller doses of atropine such as the patient was receiving.

This patient with arteriosclerotic heart disease and conduction disturbances and with Stokes-Adams attacks apparently had suffered myocardial damage and was repeatedly under exaggerated vagal effect which at times produced ventricular standstill with accelerated auricular rate and, with about equal frequency, simultaneous auricular and ventricular standstill.

Summary

1. A patient with Stokes-Adams attacks has been reported in whom simultaneous auricular and ventricular standstill has been shown to be the underlying disturbance of mechanism in about half of the attacks of which we have electrocardiographic record.

2. We have not been able to find elsewhere the record of auricular standstill in Stokes-Adams attacks unless it was preceded by prolonged ventricular asystole.

3. Atropine abolished the attacks completely and vagal stimulation is believed to have played a major role in their production.

4. The development of complete A-V block is thought to have stabilized the mechanism, enabling the attacks to be abolished by a smaller amount of atropine.

Sumario Español

1. Se ha reportado un paciente con ataques Stokes-Adams en el cual pausa auricular y ventricular demostró ser el disturbio en mecanismo en aproximadamente la mitad de los ataques en los cuales se obtuvieron trazados electrocardiográficos.

2. No hemos podido encontrar en nigun sitio trazados de pausa auricular en ataques Stokes-Adams a menos que no fuera precedida por una prolongada asistolia ventricular.

3. La atropina abolio los ataques completamente y el estímulo vagal se cree juegue un papel importante en su producción.

4. El desarrollo de bloqueo A-V completo se cree que estabilice el mecanismo, permitiendo que los ataques puedan ser abolidos por una cantidad menor de atropina.

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Stokes-Adams Seizures

Case Report of "Paroxysmal Ventricular Standstill" and Its Production by Carotid Sinus Pressure

By Ford K. Hick, M.D.

A patient presenting syncope and convulsions was shown to have spontaneous attacks of ventricular standstill without preceding or subsequent partial heart block and with the auricles beating regularly throughout. Carotid sinus pressure reproduced one such attack. This is a demonstration of nervous control in the heart below the auriculoventricular node and perhaps in the ventricle itself. Cookson's term "paroxysmal ventricular standstill" is uniquely fitting. The presence of right bundle branch block raises the question of a lesion affecting both the left and right branches of the bundle of His.

THIS CASE report presents the electrocardiographic findings in a man suffering many spontaneous periods of ventricular standstill which could be reproduced by carotid sinus pressure. Between the attacks there was no partial heart block. As his Electrocardiogram showed right bundle branch block, there may have been disease of both branches of the bundle of His.

Case Report

A man, 63 years old, entered West Suburban Hospital (#44239) on Nov. 26, 1952, as a patient of Dr. Bertha Fisher. For one week he had had numerous fainting spells and had fallen several times but had not hurt himself. He had continued working until admitted to the hospital. In the 24 hours before entrance, several attacks had occurred while he was at his office. Until this complaint started, he was well and active, walking several blocks without dyspnea or chest pain. He had no knowledge of previous heart disease.

Soon after admission, he was observed in a generalized convulsion in which he developed cyanosis. He denied any aura. The attacks came repeatedly, every few minutes. The radial pulse and heart tones disappeared before each convulsion and often disappeared for up to 10 seconds with no subsequent convulsion, in fact with no subjective sensation whatsoever. The attacks were not observed to be related to eating, straining at stool or posture. They appeared during sleep as well as while awake.

The patient was a small, slender man of 63; he was alert and cooperative. He did not appear to be sick save for the convulsions. The pulse rate was usually 88, blood pressure 170/80. He had no fever. There was no evidence of cardiac enlargement. No murmurs were heard. There were no findings of congestive heart failure. Neurologic examination added nothing. An initial white cell count was 13.600 per cubic millimeter; this fell to 11.000 in three days. Later a chest x-ray film showed the heart to be of normal size and contour.

The electrocardiogram showed a sinus rhythm with right bundle-branch block. A-V conduction time was 0.18 second. No evidence could be found of a fresh myocardial infarct. Figure 1 *A*, *B*, and *C* show the phenomenon of ventricular standstill and its termination, sometimes with reappearance of the usual ventricular complex or a ventricular ectopic beat, or ending in a convulsion, if asystole lasted 11 seconds. Note that the P-R interval was normal immediately before and after the period of asystole.

The patient was given atropine sulfate, 0.8 mg., subcutaneously at four-hour and later six-hour intervals. This appeared to reduce the frequency of the attacks. On December 3, the convulsive attacks ceased and the pulseless periods were less frequent and brief, their duration not exceeding five seconds. He was allowed progressively more activity and discharged on December 14 with the continuance of oral atropine. He had no more convulsions but had a few brief periods of faintness. He has since moved away and has not been under medical supervision. He is still living.

While on atropine and having frequent periods of spontaneous ventricular standstill carotid sinus pressure was attempted once with no effect on the rhythm of the ventricle. On Jan. 5, 1953, about three hours after his regular oral dose of atropine (0.4 mg.), an electrocardiogram still showed normal P-R interval and right bundle-branch block. At this time right carotid sinus pressure induced the ven-

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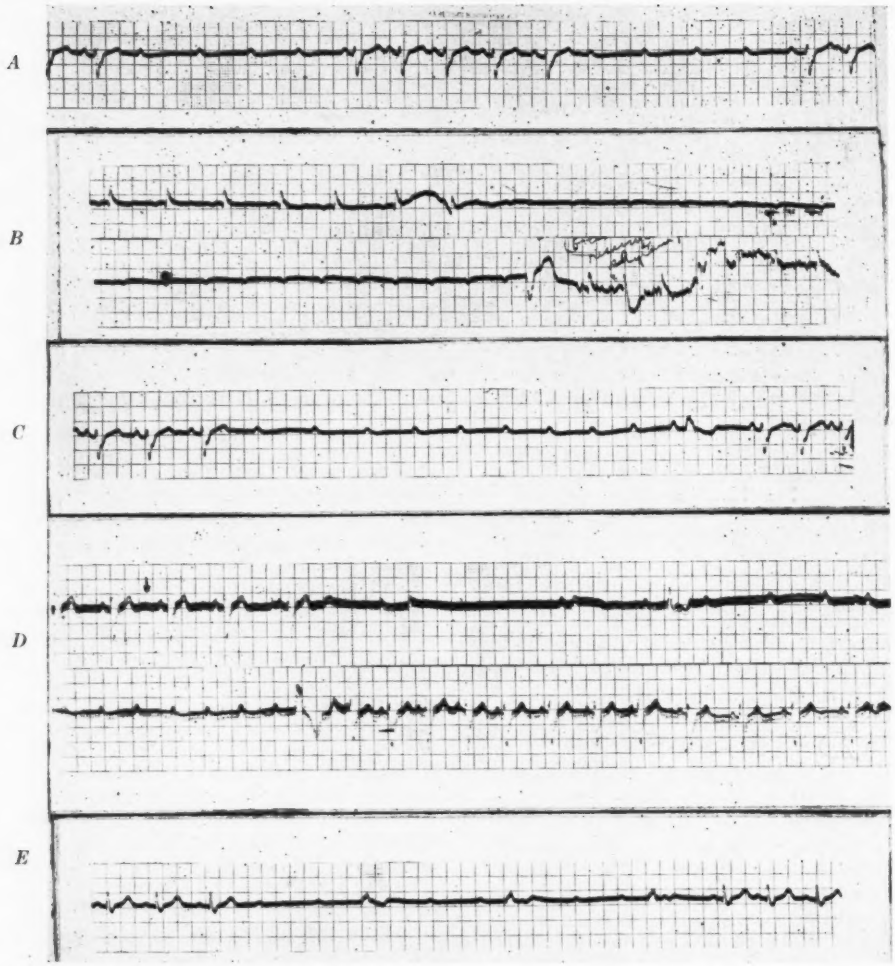

FIG. 1. (*A*) This section of lead III shows two short periods of ventricular standstill. Note the normal P-R interval before and after the pause. (*B*) Continuous record showing a spontaneous ventricular standstill ending in a convulsion. (*C*) Ventricular standstill is shown terminating after a ventricular ectopic beat. Note P-R intervals are normal immediately before and after the asystole (lead III). (*D*) Continuous record (lead III) made when carotid sinus pressure was applied (arrow) showing slowing of the auricles and ventricular standstill of 10 seconds duration. (*E*) Lead I showing appearance of an idioventricular rhythm during ventricular standstill. This occurred after adrenalin. The different pattern of the QRS complexes is perhaps significant.

tricular standstill shown in figure 1*D*. We did not choose to test the response further. This response differs from the usual cardiac standstill following pressure on the carotid sinus in which auricular and ventricular waves both disappear. In other words conduction of the impulse from auricle to ventricle is here blocked in the lower part of the A-V node or below the A-V node, following carotid sinus pressure.

DISCUSSION

The report is believed warranted because of the rarity of evidence of responses of the ventricles to nerve impulses[1] and because of the rarity of ventricular standstill without preceding or subsequent partial A-V block. Cookson[2] reported three cases of "paroxysmal

ventricular standstill" to which he gave this term. Two of his cases had normal rhythm and conduction immediately before and following the standstill. In two of his cases the attacks could be precipitated by various procedures including carotid sinus pressure. Schwartz and Eichna[3] presented records in which carotid sinus pressure produced ventricular standstill lasting long enough to induce a convulsion while the auricle kept beating. A-V conduction was initially normal, but the patient later developed heart block. Scott and Sancetta[4] described the case of a woman with complete heart block having similar convulsive episodes induced by straining at stool and reproduced by digital rectal examination. These attacks proved to be high ventricular tachycardia and fibrillation. That reflexes of visceral origin have an effect on the bundle of His or on the ventricular muscle can be inferred from the case of Scott and Sancetta and from the one here reported. The possibility exists that such reflex effects may cause sudden death. Perhaps hearts susceptible to such exaggerated reflex responsiveness were not normal and the abnormalities present may have rendered them particularly susceptible to such reflexes.

Perhaps our patient really has disease of both branches of the bundle of His. Figure 1*E* shows the pattern of altered intraventricular conduction during idioventricular rhythm. This tracing was made early in his illness after the administration of adrenaline, 0.5 cc. subcutaneously. The pattern of the ventricular complex is quite different at the slow rate. Hein and Sanazaro[5] reported a case of left bundle-branch block which consistently reverted to normal intraventricular conduction when slowed by carotid sinus pressure. They reviewed the literature on vagus action on intraventricular conduction.

Summary

A patient presenting syncope and convulsions was shown to have spontaneous attacks of ventricular standstill without preceding or subsequent partial heart block and with the auricles beating regularly throughout. Carotid sinus pressure reproduced one such attack. This is a demonstration of nervous control in the heart below the auriculoventricular node and perhaps in the ventricle itself. Cookson's term "paroxysmal ventricular standstill" is uniquely fitting. The presence of right bundle branch block raises the question of a lesion affecting both the left and right branches of the bundle of His.

Sumario Español

Un paciente presentando el cuadro de síncope y convulsiones demostró tener ataques espontáneos de pausa ventricular sin ser precedidos o seguidos de bloqueo parcial cardíaco y con los aurículos contraiéndose regularmente durante el ataque. Esto es una demostración de control nervioso en el corazón inferior al nódulo atrioventricular y quizás en el ventrículo propio. El término de Cookson "pausa paroxística ventricular" es singularmente apropiado. La presencia de un bloqueo de ramo derecho suscita la posibilidad de una lesión lesión afectando ambos ramos izquierdo y derecho del haz de His.

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Peculiarities of the African's Electrocardiogram and the Changes Observed in Serial Studies

By H. GRUSIN, M.B., B.CH., M.R.C.P. (LOND.)

Among African medical patients with and without heart disease about 63 per cent are found to have electrocardiograms which are abnormal by accepted standards. Twenty-two per cent of a group of healthy African nurses show the same peculiarities. Over a period of months or years the electrocardiograms show spontaneous changes. Clinical and postmortem evidence indicates that the electrocardiographic changes are not related to organic heart disease. It is suggested that these electrocardiograms may be of a juvenile type or alternatively that they may be attributable to some obscure metabolic factor of nutritional origin.

THE ELECTROCARDIOGRAM of occasional healthy American Negroes is known to show inversion of T waves in precordial leads,[1] and similar findings have been reported in the South African Bantu (African).[2] In this study evidence is presented that the electrocardiogram of the African differs in two main respects from that of a white man. First, patients without heart disease show peculiarities not only of the T wave but also of the S-T segment and P wave, and second, a series of striking changes takes place in the electrocardiogram for which no reason is apparent.

MATERIAL AND METHODS

The patients on whom these studies were made were urbanised Africans accustomed to living under squalid conditions and subsisting on a badly balanced diet. Fifty healthy young female African nurses who were adequately housed and fed served as a control group. Electrocardiograms were recorded from the nurses and from patients with and without heart disease. A random sample of subjects showing these peculiarities were selected from each group for further study. Tracings were recorded daily for the first two weeks and thereafter at weekly intervals for 1 to 12 months, and the effects of drugs and certain maneuvers on the electrocardiogram were also studied.

RESULTS

At least 63 per cent of 159 consecutive medical patients admitted to the wards and 22 per cent of healthy nurses showed electrocardiograms which deviated significantly from the accepted normal (table 1). For purposes of description these have been classified into three patterns on the basis of S-T deviation in precordial leads.

Pattern 1. S-T Depression and Inverted T Waves in Precordial Leads (fig. 1A)

Incidence. These electrocardiographic features were found in 33.9 per cent of 159 medical patients, in 34.1 per cent of patients with heart disease and in 14 per cent of healthy nurses (table 1). They occurred in adults of all ages and both sexes. Twenty one patients showing this pattern were selected for follow-up studies and of these only seven had heart disease.

Precordial Leads (fig. 1A). In a typical right ventricular surface lead (V_2) the end deflection consisted of a deeply inverted T wave with depression of J and an S-T segment bowed upwards to form a wide shoulder; the whole deflection was asymmetrical with a longer distal limb which ended in a rounded hump before settling on the isoelectric line.

In 17 patients these features were most marked in right ventricular surface leads, in three they were seen in all precordial leads and in one they were confined to left ventricular surface leads (fig. 2*A*, *C*, *D*).

Standard and Augmented Unipolar Extremity Leads (fig. 2A, C, D). When all precordial leads or only left ventricular surface

From the Baragwanath Hospital and the University of the Witwatersrand, Johannesburg.

TABLE 1.—*Comparative Incidence of Patterns in Three Groups of Subjects*

	Total	Pattern 1	Percentage	Pattern 2	Percentage	Pattern 3	Percentage
Random group of patients; consecutive medical admissions	159	54	33.9	40	25.2	7	4.4
Patients with heart disease; consecutive admissions; undigitalised	41	14	34.1	12	29.3	—	—
Healthy nurses	50	7	14	2	4	2	4

leads showed S-T depression and T wave inversion, unipolar extremity leads and standard leads reflected these features. In leads facing the cavity or the back of the heart the T wave was always upright and the S-T segment either isopotential or elevated (4 of 21 cases). When only right ventricular surface leads were affected unipolar extremity leads and standard leads were hardly abnormal (17 of 21 cases).

Serial Changes (*figs. 1A to E, 3 A to F*). Within one to three weeks the end deflection began to change. The inversion became shallower and the S-T segment, taking off higher, was now boldly curved above the isoelectric line giving the T wave a cove-plane appearance. Days or weeks later more and more of the S-T segment appeared above the isoelectric line and the inversion became still shallower. From this stage the evolution of the T wave followed one of two courses. In 17 patients it never became upright during the period of observation but remained inverted and continued to change in shape, being deeper, shallower or almost upright on different occasions (fig. 3); in one patient it was still showing changes a year after his admission to hospital (fig. 2 A, B). In four patients the T wave became upright in periods ranging from 14 to 49 days; when right ventricular surface leads were involved the inversion disappeared from V_3 first and V_1 last, and when both ventricular surface leads were affected the inversions disappeared from both at the same time or independently. In two of the four patients in whom the T wave had become upright it was found to be inverted again within a month, and similar cycles of T-wave inversion and recovery were found in the past records of patients for periods as long as three years.

The inverted T waves were not always as gross as those illustrated in the pictures. The first electrocardiogram recorded from these 21 patients revealed a deeply inverted T wave in only nine and a "cove-plane" or shallow inverted T in the remaining 12. Although the serial changes described above apply to both types, there was one obvious difference in be-

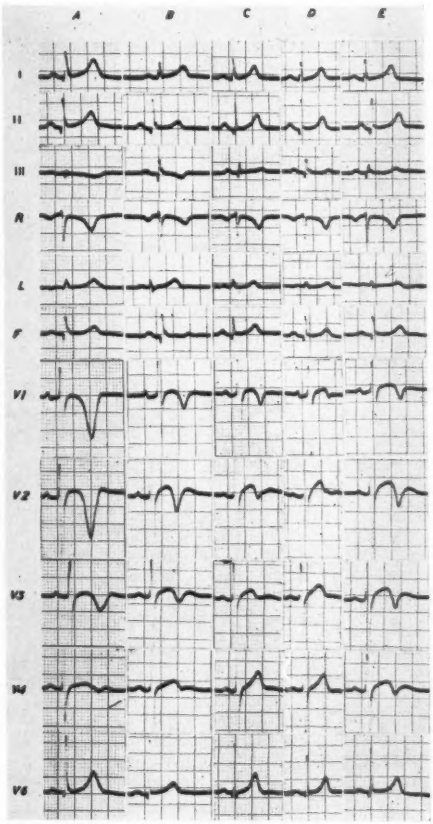

FIG. 1. Male, aged 30, with lobar pneumonia. No heart disease. *A* to *E* made at 10-day intervals. Pattern 1 more or less confined to right ventricular surface leads.

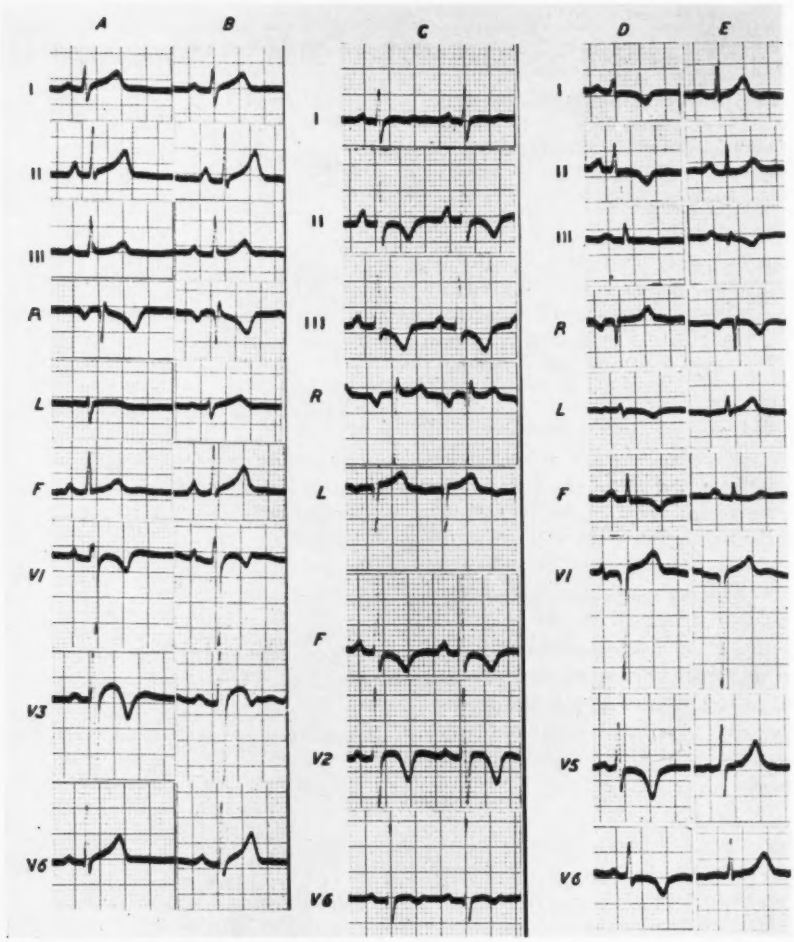

FIG. 2. (*A*) Male aged 14, with petit mal. No heart disease. (*B*) One year later. The electrocardiogram had never been normal during this time. Pattern 1 confined to right ventricular surface leads; standard and limb leads normal. (*C*) Male, aged 24, with typhoid fever. No heart disease. Both ventricular surface leads show inverted T waves; standard and limb leads abnormal. The S-T segment is elevated in aV_L. (*D*) Male, aged 30, with pleural effusion. No heart disease. Pattern 1 confined to left ventricular surface leads; standard leads and limb leads abnormal. (*E*) Two weeks later.

havior between deeply inverted T waves and shallow ones. The deeply inverted T wave changed gradually and reached the coveplane stage in one to three weeks. From this point it changed more rapidly and, once most of the S-T segment lay above the isoelectric line, the deflection became labile and capricious; nervousness on the part of the patient, a sudden noise or the sight of an hypodermic syringe might make it deeper or shallower. In continuous tracings it showed mild changes from hour to hour and in daily records it might appear deeper on one day, shallower or almost upright on the next.

Other Studies. Exercise, deep inspiration or expiration, change in the patients' posture, the inhalation of amyl nitrite and intravenous injection of atropine 0.9 mg. had little or no effect on deeply inverted T waves. When the initial inversion of the T wave was shallow,

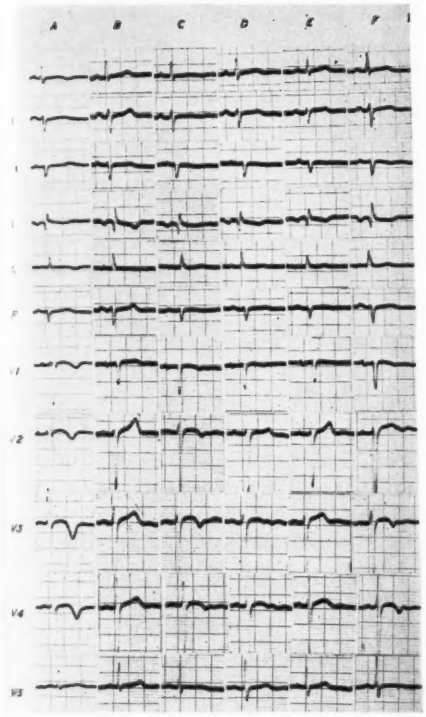

FIG. 3. Male, aged 27, with pellagra. No heart disease. *A* to *F* made over a period of 3½ months. P waves are bifid in leads III, aV_F, V_2–V_4.

however, the same procedures, and particularly intravenous atropine, changed the form of T which became less inverted or completely upright. Neither deep nor shallow inverted T waves were affected by carotid sinus pressure.

Pattern 2. S-T Elevation and Tall T Waves in Precordial Leads (fig. 4)

Incidence. These electrocardiographic features were found in 25.2 per cent of 159 medical patients, in 29.3 per cent of patients with heart disease and in two nurses (4 per cent) (table 1). Eighteen patients showing this pattern were selected for follow up and of these only two had heart disease.

Precordial Leads. In a typical left ventricular surface lead (V_5) the terminal deflection showed elevation of the S-T segment and a tall bold T wave with a slowly rising ascending limb and a sharply falling distal limb ending in a U wave. These features were seen in left ventricular surface leads in every case but only twice in right ventricular surface leads (fig. 5).

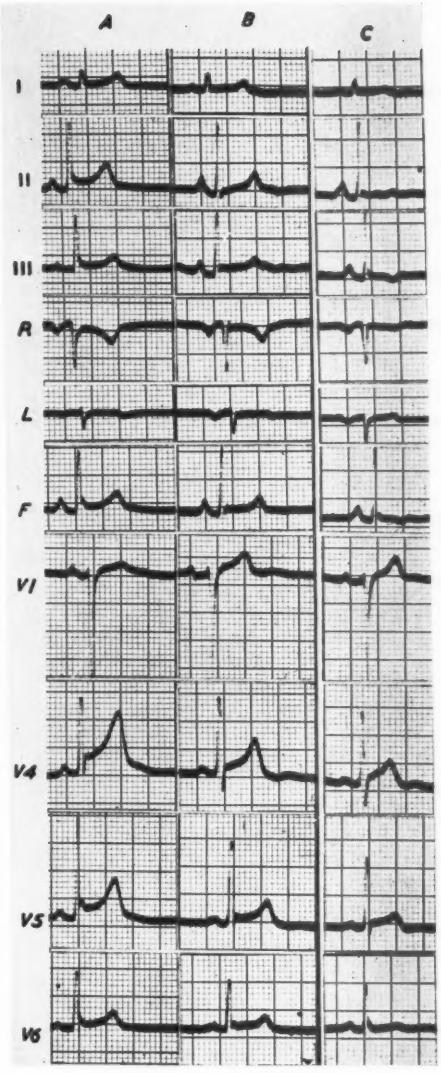

FIG. 4. Male, aged 30, with lobar pneumonia. No heart disease. *A* to *C* obtained at intervals of 2 weeks. S-T elevation in left ventricular surface leads, in aV_F and standard leads II and III; lead aV_R shows S-T depression and deep inversion of T.

Standard Leads and Augmented Unipolar Extremity Leads. The S-T elevation was usually

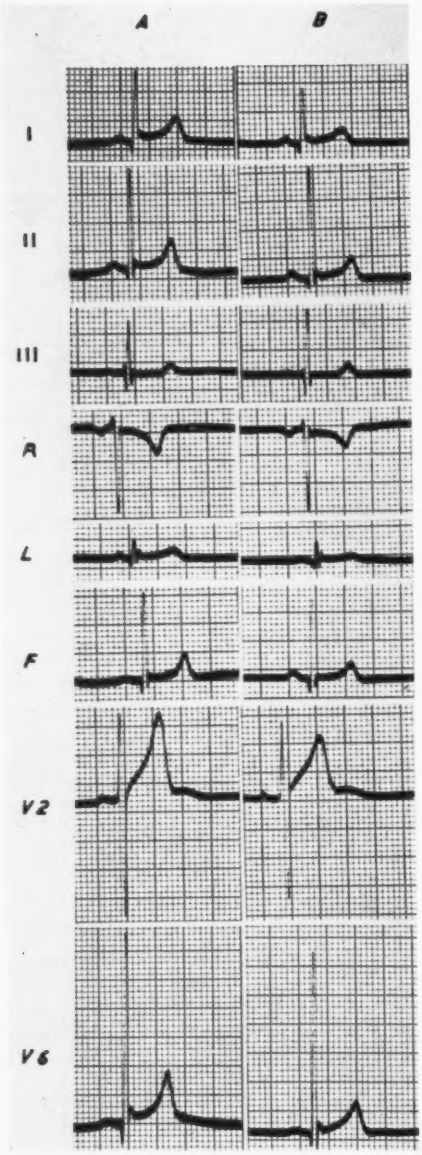

FIG. 5. Male, aged 23, with acute bronchitis. No heart disease. *A* obtained on admission and *B* six weeks later. S-T elevation and tall T waves in both right and left ventricular surface leads; the R wave in V_6 has apparently become shorter.

apparent in unipolar extremity leads tapping the left ventricular surface and was always reflected in standard leads I and II and usually in lead III. Leads facing the cavity or the back of the heart showed striking S-T depression and deeply inverted T waves.

The QRS Complex. Some subjects showing this pattern had unusually tall R waves in left ventricular surface leads (fig. 5). Excluding patients with heart disease, the tallest R wave measured 35 to 47 mm. in three patients, 25 to 30 mm. in five patients, and ranged between 15 and 25 mm. in the rest. The height of the R waves was not related to the degree of S-T elevation nor to the height of the T wave and the QRS complexes were usually less than 0.05 second in width.

Serial Changes. The end deflection changed in every case, but sometimes so slowly that a difference was only appreciable after weeks or months. In five patients the electrocardiogram came to resemble the accepted normal in 12 to 60 days, but in the remaining 13 patients the S-T and T deviations were still present 6 to 12 months later. During this period the electrocardiogram showed many changes. The degree of S-T elevation was always varying and the shape of the T wave was always changing, at times being rounded and at others reverting to its bold, peaked form; in three patients it became flat or mildly inverted while the S-T segment was still elevated Factors tending to raise the heart rate, such as anxiety on the part of the patient, usually produced a slight drop in the level of the S-T elevation and in the height of the T wave.

Two patients with normal blood pressures and hearts of normal size showed R waves measuring 45 mm. in V_5 on numerous occasions during a period of a year. At other times the R waves appeared to have lost 5 to 10 mm. in height (fig. 5), but over such a long period of time it was impossible to be sure that this reduction in height was not due to some factor causing a change in the position of the heart relative to the electrode.

The pattern did not always show features as marked as the examples illustrated. All gradations were seen to graphs which would have been accepted as normal if previous or subsequent records had not been available. The elevation of J in left ventricular surface leads ranged from 1 to 4 mm. and the height of the T wave from 7 to 17 mm.; lesser degrees of

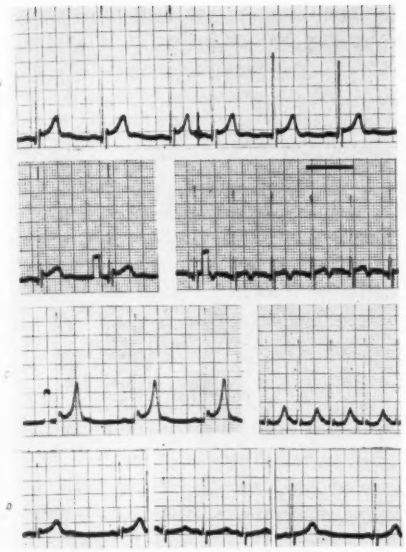

FIG. 6. (A) Male, aged 27, with acute bronchitis. No heart disease. Lead V_5, normal standardization. Reduction in size of R wave during deep inspiration. (B) Same patient as in *A*. Standardization 1 mv. = 7 mm. Control strip of V_5 on left and effects of amyl nitrite on right. Respiratory variation is seen and inspiration is marked. (C) Male, aged 20, with tuberculous cervical adenitis. No heart disease. Control strip of V_5 on left and effects of amyl nitrite on right. (D) Male, aged 30, with pneumonia. No heart disease. Control strip of V_5 on left; center strip, one minute after inhalation of amyl nitrite; strip made 10 minutes later on right. Neither the S-T segment nor the R wave have recovered their previous height.

S-T elevation were difficult to appreciate in right ventricular surface leads and could only be diagnosed in retrospect as the electrocardiogram changed.

Other Studies (*fig. 6*). The inhalation of amyl nitrite usually reduced the degree of S-T elevation and the height of the T wave which sometimes became inverted; within two or three minutes, as the heart rate slowed, the end deflection usually reverted to its original form. When amyl nitrite caused an appreciable drop in the height of T, the R wave also became shorter.

Similar effects on the end deflection and the R wave were observed after exercise (running) and after a deep inspiration but not with postural changes or carotid sinus pressure.

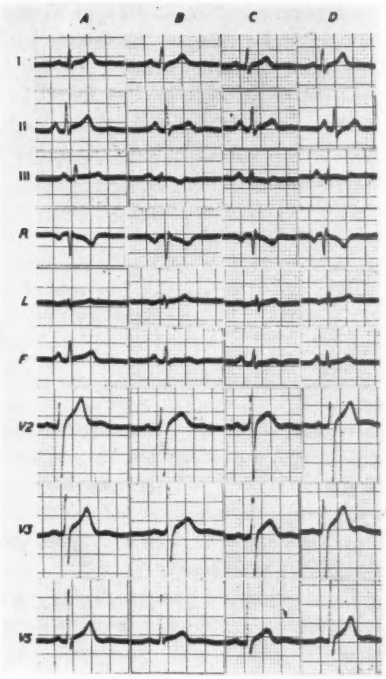

FIG. 7. Male, aged 41, with acute bronchitis. No heart disease. *A* to *D* obtained at weekly intervals.

Pattern 3. Rounded or "Flat" T Waves in Precordial Leads (*fig. 7*)

The two patterns already described were striking and easily detected but in some patients without heart disease the electrocardiogram showed more subtle changes. In these the precordial T wave though upright had lost its contours, the concavity of the upstroke was ironed out and the apex rounded; all gradations were seen from such rounded T waves to completely "flat" ones. The tracings showed changes over the weeks; in some, the T wave gained height and recovered its lines and in others the pattern of T inversion or S-T elevation supervened. Pattern 3 was recognizable in 4.4 per cent of the random group of medical patients but the incidence of lesser degrees of change could not be accurately assessed.

Combined Patterns

In a few patients patterns 1 and 2 were seen together in the same electrocardiograms, leads V_1 to V_4 showing S-T depression and in-

verted T waves and leads V_5 and V_6 S-T elevation and tall T waves. In the majority of patients with pattern 1, however, S-T elevation, if present at all, was only found in leads facing the cavity or the back of the heart and not at "free" ventricular surfaces anteriorly, laterally or posteriorly.

Other Data

The three patterns were seen at rapid and slow heart rates. Sinus rhythm was the rule except in four patients who showed nodal rhythm. The P-R interval lay within normal limits. The electrical position of the heart was horizontal in 15 patients, vertical in 23 and "indeterminate" in one. The corrected Q-T interval (Q-Tc)[3] in 10 patients ranged between 0.34 and 0.43 second but the length of the interval did not vary significantly with changes in the end deflection. The QRS complex showed no abnormality in patterns 1 and 3.

The P wave showed changes. In 10 patients it lost its sharp outline and became rounded, indistinct or split (fig. 3). In some patients these changes were seen in all leads but in others they were confined to standard or precordial leads.

Relation between the Electrocardiogram and the Clinical State

All the nurses and the majority of patients showing these patterns had no evidence of heart disease by clinical or radiologic standards nor were the patterns encountered more frequently in cardiac patients than in the random group of medical admissions. (See table 1.) Usually there was no association between the nature and severity of the patients' medical illness and his electrocardiographic changes. Amongst the nurses the patterns were found less frequently and the deviations were not as gross as those seen amongst the medical patients.

Postmortem and Other Evidence

Postmortem evidence was obtained from two patients who had shown one of the two main patterns in their electrocardiogram during life. One had died of pellagra and the other of a spinal tumor. Detailed macroscopic and microscopic section revealed no abnormality of the heart, coronary vessels or lungs. In several other patients showing one or other pattern in their electrocardiogram during life, routine postmortem examination failed to reveal a cardiac lesion.

In two nurses and in 10 patients the blood potassium and calcium levels and the carbon dioxide combining power were estimated and repeated at intervals during the evolution of the electrocardiographic changes. The results were always within normal limits.

Discussion

There is a marked resemblance between the end deflections described here and those seen in various types of organic heart disease. The appearances of the S-T segment and T wave mimic those of myocardial infarction, left ventricular hypertrophy, acute cor pulmonale and acute pericarditis, yet in these African subjects no organic damage has been found in the heart at postmortem examination to account for these features. It must be assumed, therefore, that they are of a functional nature similar to those which have been produced experimentally by physical and chemical agents.[4]

Electrophysical considerations aside, the nature of the lesion remains to be explained. Littmann,[1] who described similar precordial T-wave inversions in healthy American Negroes, attributed them to the infantile bodily habitus of his subjects. Brink[2] found inversion of precordial T waves from V_1 to V_3 in 5 per cent of healthy Africans and considered that they were due to vagotonia.

In this study no correlation is found between the electrocardiographic patterns and the electrical position of the heart or the bodily configuration of the patient. When the T wave is at a labile stage the changes which occur spontaneously and those which follow immediately on an injection are probably due to nervous factors. On the other hand there are several features of these patterns which cannot be explained on a neurogenic basis, namely, that the deviations are gross and may

remain unchanged for weeks, that they occur at rapid and slow heart rates and are unaffected by carotid sinus pressure.

The S-T segment and T-wave changes of these patterns though they sometimes disappear often linger in the electrocardiogram for months or years. With what other known electrocardiographic patterns can they be compared? Those changes caused by drugs or associated with disordered metabolic states are transient and disappear when the operative factor is removed or corrected.[5] Possibly the closest parallel to these patterns is to be found in the precordial T-wave inversions of children which exist for years and are found to have disappeared in adult life. Various explanations have been advanced to account for these inverted T waves. On the one hand they have been ascribed to physical factors such as the electrical position of the heart in childhood and on the other to chemical differences between the two ventricles.[5] It is tempting to speculate that the electrocardiogram of the African may be of a juvenile type in the developmental sense and it would be interesting to know whether the T waves of children at the time when they become upright show the same lability and responses as do those described here.

Finally in assessing any departure from the accepted normal in Africans the problem of undernutrition is an ever present bogey. Even when apparently healthy, many of them suffer from occult liver disease,[6] and it is possible that some metabolic factor produces these electrocardiographic changes by acting locally on the heart or by causing a change in the patient's internal environment.

Summary

1. At least 63 per cent of 159 African patients admitted to medical wards and 22 per cent of apparently healthy African nurses showed electrocardiograms which deviated from the accepted normal.

2. Spontaneous fluctuations occurred in these electrocardiograms over a period of 1 to 12 months.

3. The changes observed have been arbitrarily classified into three patterns.

4. The electrocardiographic peculiarities were apparently not due to organic heart disease.

5. The etiology of these changes is unknown and theories as to their causation are discussed.

Acknowledgments

I wish to express my thanks to Drs. B. van Lingen, W. H. Craib and J. C. Gilroy for their advice in the preparation of the manuscript, to Dr. P. S. Kincaid-Smith for mounting the electrocardiograms and for much help in other ways, to Dr. J. Higginson for examining the sections of the hearts, and to Protea Distributors Ltd., Johannesburg, for the loan of a Cambridge Cardiette.

Sumario Español

1. Por lo menos 63 por ciento de 159 pacientes africanos admitidos a los pabellones médicos y 22 por ciento de enfermeras aparentemente saludables mostraron electrocardiogramas con desviación del normal aceptado.

2. Fluctuaciones espontáneas ocurrieron en estos electrocardiogramas sobre un período de 1 a 12 meses.

3. Los cambios observados han sido arbitrariamente clasificados en 3 patrones.

4. Las peculiaridades electrocardiográficas no fueron aparentemente debidas a cambios orgánicos en el corazón.

5. La etiología de estos cambios se desconoce y las teorías sobre la causa se discuten.

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Electrocardiographic Leads

III. Synthesis

By Richard McFee, M.S., and Franklin D. Johnston, M.D.

This concluding paper of a series of three on electrocardiographic leads indicates how leads that should be superior to many now in use may be constructed. The design of leads to obtain accurate representations of the mean cardiac vector in the usual planes of reference, methods for the improvement of several of the conventional leads, and a unipolar lead of a new type are emphasized.

In the first and second papers of this series[1, 2] the concept of the "lead field" was introduced, and it was shown how the behavior of leads may be determined by an analysis of their lead fields. In this final paper, methods for the construction of leads that should be superior to those in common use are described.

Although some of these methods are complicated, and to a certain extent mathematical, their purpose is practical. They should result in leads of exceptionally high accuracy. For example, when the precision of the standard leads is not adequate, these methods show where electrodes may be placed and how they may be interconnected so that greater accuracy is attained. In cases where unipolar electrocardiograms are being taken and the exploring electrode is on the back or sides, rather than on the anterior chest, the methods show how the central terminal may be modified so that it remains indifferent. Again, using these methods, a lead can be built which yields an accurate measure of the sagittal component of the heart vector.

These methods for synthesizing leads are variations of a single basic procedure which is as follows. First, the exact nature of the desired lead is specified by describing what its field in the heart ought to be. This is usually done by modeling the lead after a "prototype" lead in an infinite homogeneous conductor. Second, a lead is constructed which actually produces such a field, or a close approximation to it, taking into account the irregular shape and conductivity of the human body.

Two basic methods for the design of leads are presented. The first and more practical approach relies on the combination of several leads in such a fashion that undesirable aspects of the field, such as incorrect general direction, flare and curvature are systematically cancelled out. This method ("synthesis of leads by combination") is essentially a generalization of the methods for correcting the direction of lead vectors which have already been worked out by Burger and vanMilaan,[3] by Wilson, Bryant and Johnston,[4] and by Becking, Burger and vanMilaan.[5]

The second more mathematical approach attempts to determine the precise nature of the lead field on the body surface which would produce the correct field in the heart. This surface field is then approximated by connecting surface electrodes to the two terminals of the lead through suitable networks of resistors. The success of this second method ("synthesis of leads by adjustment of the lead field current at the body surface") is due to the fact that it is mathematically much easier to find the surface currents necessary to produce a specified field in a conductor than it is to find the field within the conductor resulting from specified surface currents.

The first part of the paper, which deals with the first approach, begins with a procedure for obtaining a set of three terminals whose lead vectors form an Einthoven triangle; that is to say, three terminals whose three leads produce fields at the center of the heart having the same direction that the fields of the standard leads would have if all of Einthoven's assump-

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tions were correct. Following this, the construction of a simple lead for obtaining all three components of the heart vector from a set of three independent leads with one common electrode is discussed. Next, means of correcting the curvature of the fields of lead I and the central terminal chest leads are taken up.

In the second part of the paper the general idea of the second approach is illustrated by a qualitative example which shows how any lead for obtaining the sagittal component of the heart vector *must* be constructed. Then a method is presented for the construction of "perfect" heart vector leads for a "body" which is a homogeneous box, and it is indicated why this same general procedure may be employed to obtain such leads when the body is assumed a homogeneous conductor of any shape containing a spherical or ellipsoidal heart of greater conductivity than its surroundings.

In the latter portion of this part of the paper similar methods are applied to the problem of the construction of a perfect "indifferent electrode." It is shown here that it is theoretically possible to obtain a type of unipolar lead for which the *effective* location of the exploring electrode is within the body, close to the surface of the heart, despite the fact that all of the electrodes of the lead are actually on the body surface.

The third part of the paper discusses limitations to the synthesis of leads. Here, a simple demonstration shows that it is impossible to construct a lead whose voltage is influenced by the electromotive force (EMF) within a single small region of the heart. This emphasizes the extremely important fact, pointed out by numerous investigators, that one cannot get a completely detailed picture of the electromotive forces of the heart from measurements of the potentials outside of it. Another problem that is considered is the possibility of constructing a lead with a perfectly uniform or radiating field in a conductor (such as the body) whose conductivity variations are not of a simple type.

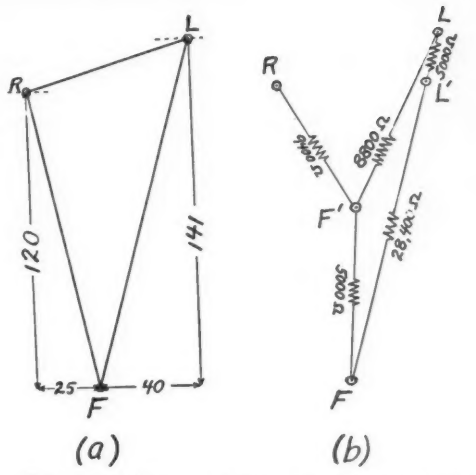

FIG. 1. (*a*) Burger triangle for standard leads. (*b*) Network for transforming it into an Einthoven triangle.

SYNTHESIS OF LEADS BY COMBINATION

Three Terminals whose Lead Vectors Form an Einthoven Triangle

Experiments with cadavers and normal subjects, with electrolytic models, fluid mappers and conducting paper manikins, all indicate that at the center of the heart the Burger triangle has more or less the shape* shown in figure 1*a*. Assuming the accuracy of this, it is possible to find three terminals, connected to the electrodes of the arms and left leg by resistors, which are associated with an equilateral Burger triangle. A graphic procedure for doing this is illustrated in figure 2. In step 1 of this figure a line is drawn horizontally from R until it intersects the opposite side at point L'. The distances between this point, L', and the two ends, L and F, of the line determine the ratio of the two resistances r_1 and r_2, as shown in step 2. In step 3 a compass is used to find the point F', which completes the equilateral triangle having the line RL' as its top. A straight line drawn through R and F' extended to the opposite side, LF, determines an intersection

* The exact dimensions of the triangle were so chosen that they are the same as those found by Burger and vanMilaan. (Reference 2, part II, page 157.)

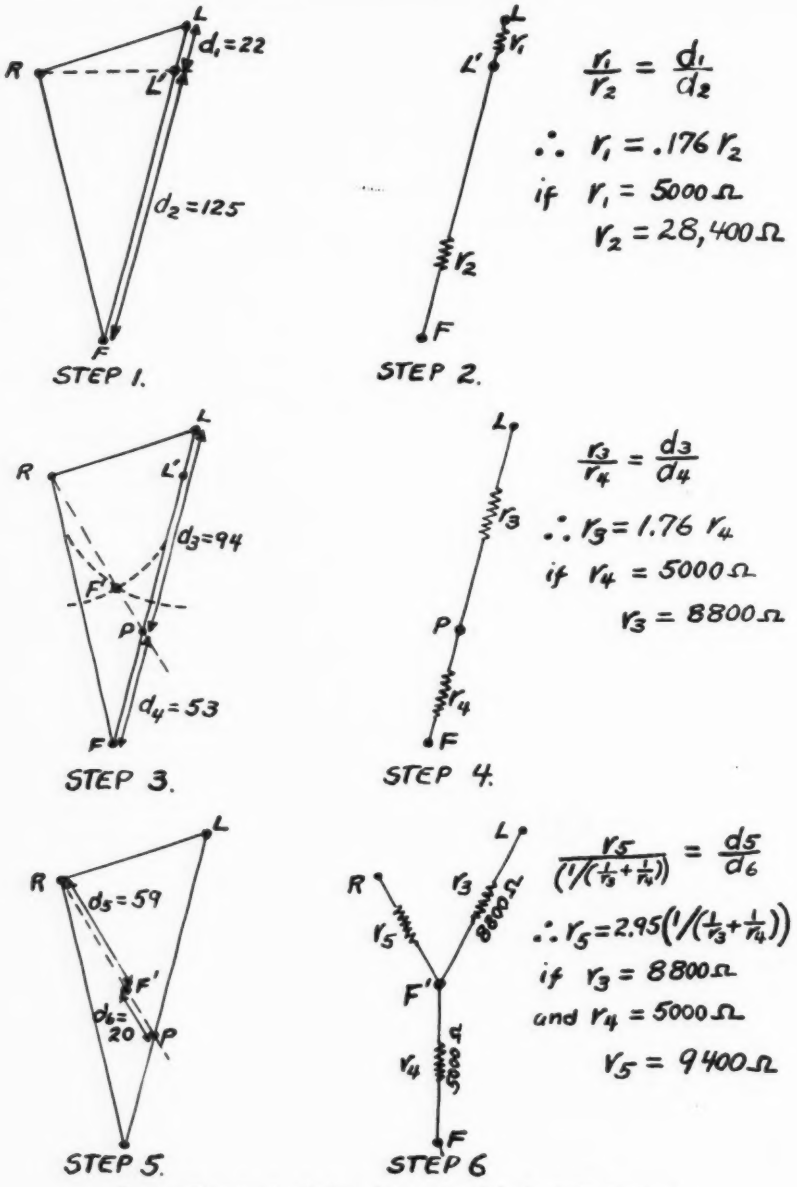

FIG. 2. Steps in the design of the network in fig. 1 (*b*). See text.

point, P, and in step 4 this point is obtained electrically with resistors r_3 and r_4. The addition of the fifth resistor, r_5, in step 6, in accordance with measurements of d_5 and d_6 made in step 5 produces the desired third terminal, F'.

This procedure involves an important rule which applies when one knows the lead vectors of several electrodes (or terminals) with respect to a common or reference electrode, and wishes to find the vector associated with a tap on a resistor (of a relatively high

value) connected between two of these electrodes. This rule, which was pointed out both by Wilson, Bryant and Johnston and by Burger and vanMilaan, states that the tap will have the same position on a straight line joining the tops of the vectors associated with the two electrodes as it has on the resistor. This justifies, in figure 2, the relations

$$\frac{r_1}{r_2} = \frac{d_1}{d_2}, \quad \frac{r_3}{r_4} = \frac{d_3}{d_4}, \quad \frac{r_5}{\left[1 \Big/ \left(\frac{1}{r_3} + \frac{1}{r_4}\right)\right]} = \frac{d_5}{d_6} \qquad (1)$$

A proof of this important principle is given in the Appendix. Note that in step 6 the parallel resistance of r_3 and r_4 had to be taken into account.

One should also note that the connection of resistor r_5 between R and F' will change the magnitude but not the direction of the lead vector. The effect of the added resistor, of course, is simply to shunt off some of the lead field current which would otherwise pass through the body.

The total circuit is that shown in figure 1*b*. Here the resistors have been made sufficiently large so that the leads will be insensitive to variations of contact resistance, and will have negligible influence on the fields of the body. The average length of these three new lead vectors can be made equal to the average length of the vectors of the original triangle by increasing the sensitivity of the electrocardiograph from 1 cm. per millivolt to 1.91 cm. per millivolt. This will keep the average voltage deflection produced by the three leads the same as it was before.

Obtaining the Components of the Heart Vector from a Set of Four Electrodes

In the preceding section we have seen how the direction of the lead field at the center of the heart may be adjusted through the use of external resistors. This example, however, was a two dimensional one. Let us now consider how the same thing may be done with the three components of the lead field using a set of four electrodes.

Suppose, for example, that experiments have been carried out by methods like those discussed in a previous paper of this series[2] to find the exact values of the lead fields at the center of the heart for the following three leads; *RF*, *LF* and *SF*, where R is the right arm electrode, L the left arm electrode, F the left foot electrode and S is a fourth electrode whose voltage is influenced considerably by the sagittal component of the electromotive forces.* Suppose further that these experiments yield the following results.

$$\begin{aligned} \vec{J}_{FR} &= 8\,\vec{i}_V + 4\,\vec{i}_T + \vec{i}_S \\ \vec{J}_{FL} &= 12\,\vec{i}_V - 8\,\vec{i}_T - 2\,\vec{i}_S \\ \vec{J}_{FS} &= 8\,\vec{i}_V - 2\,\vec{i}_T - 16\,\vec{i}_S \end{aligned} \qquad (2)$$

where $\vec{J}_{FR}$, $\vec{J}_{FL}$, $\vec{J}_{FS}$ are the lead field current densities associated with leads *FR*, *FL*, and *FS*, and 1_V, 1_T, and 1_S are unit vectors in the vertical, transverse, and sagittal directions respectively. How can one combine these three leads to produce a fourth lead whose lead field at the center of the heart is directed in any one of these reference directions?

The first thing to do is to find a combination of the three leads which cancels out the two undesired components of the lead field at the center of the heart. This can be done in the following way. First, find two combinations each involving a pair of leads for which one of the undesired components has been eliminated. For example, in this case

$$\begin{aligned} \vec{J}_{FR} - \vec{J}_{FS} &= 6\,\vec{i}_T + 17\,\vec{i}_S \\ \vec{J}_{FL} - \tfrac{3}{2}\,\vec{J}_{FS} &= -5\,\vec{i}_T + 22\,\vec{i}_S \end{aligned} \qquad (3)$$

Here the vertical component $\vec{i}_V$ has been removed. Next, combine these two in such a fashion that the remaining undesirable component is cancelled out; that is

$$\begin{aligned} &5\,(\vec{J}_{FR} - \vec{J}_{FS}) + 6\,(\vec{J}_{FL} - \tfrac{3}{2}\,\vec{J}_{FS}) \\ &\quad = 217\,\vec{i}_S = 5\,\vec{J}_{FR} + 6\,\vec{J}_{FL} - 14\,\vec{J}_{FS} \end{aligned} \qquad (4)$$

This equation states that if a current of 5, 6 and -14 amperes† enters the *RF*, *LF* and *SF* leads respectively, then the resultant field at the center of the heart will be directed in an

* The nature of this electrode is described later in this paper, page 873.

† This could just as well be milliamperes, the units are not important.

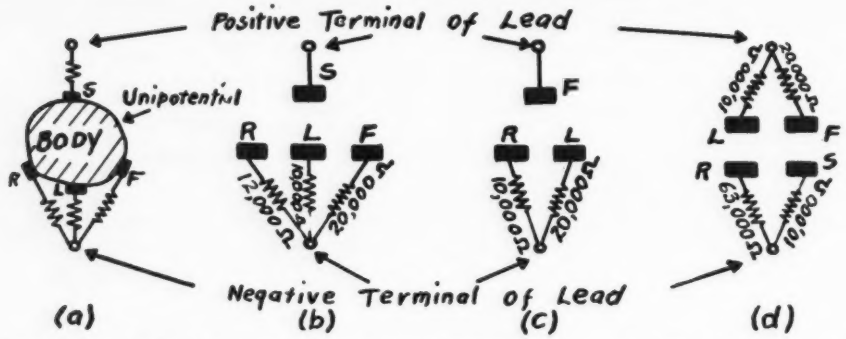

FIG. 3. Four-electrode networks. These networks illustrate the method. They are not based on experimental data.

anterior-posterior direction. Under these circumstances the current entering the body through the R, L, S and F electrodes, taken by themselves, will be 5, 6, −14 and 3 amperes respectively. The problem now is to design a resistor network which, when connected to a single source of current, will cause currents having these same relative magnitudes to enter the four electrodes R, L, S and F, since it is clear that the voltages produced in such a lead by EMF's at the center of the heart will be proportional only to the sagittal components of those EMF's.

The procedure involved here is a simple one. Electrodes carrying current which leaves the body, in this case S, are connected to the positive terminal of the lead, and electrodes having current entering them, here R, L and F, are connected to the negative terminal of the lead. The size of the resistors is adjusted so that the current splits up into the desired proportions. To do this, all resistors are first made large enough so that the potential produced between any two electrodes on the body by the lead field current is negligible compared to the voltage drop across the resistors themselves. When this is done, all the electrodes will have essentially the same potential, and the situation can be represented electrically by the diagram shown in figure 3*a*.

This diagram makes the method for adjustment of the current values quite apparent. Take, for example, the resistors between the negative terminal of the lead and the common junction representing the body. The voltage across all three of these resistors will be the same, and thus the current through each will be, by Ohm's Law, inversely proportional to the resistance of each. Thus, to make the current flowing into the R electrode $\frac{5}{3}$ times as great as the current flowing into the F electrode, the resistance connected to the R electrode must be equal to $\frac{3}{5}$ that of the F electrode. In a similar way the resistance of the L electrode is made equal to $\frac{1}{2}$ of the resistance of the F electrode. The complete circuit for obtaining the sagittal component of the electromotive forces, then, is shown in figure 3*b*. This figure also shows the circuits for obtaining the vertical (*c*) and transverse (*d*) components of the electromotive forces. Note that in these last cases two and four, rather than three resistors are needed.

In general, the procedure may be summarized as follows.* (1) Find the combination of the leads which produces the desired field. (2) From this find the value of the field current flowing into or out of each electrode. (3) Connect, through resistors, all the electrodes with outflowing current to the positive terminal of the lead, and all electrodes with inflowing current to the negative terminal of the lead. Make the relative conductances of each resistor equal to the relative intensities of the current flowing in or out of the electrodes associated with them.

This procedure is a very basic one. All methods of synthesizing leads discussed in this paper, regardless of the number of electrodes

* A similar procedure has been worked out by Burger and his associates.

involved, depend on it. Note in particular that the procedure will succeed with any combination of leads whatsoever. This means that any linear combination of leads can be obtained with a resistor lead and one amplifier. This is important because in most cases it is more practical to combine the leads before rather than after amplification.

Correction of Curvature and Flare

Just as the error in the general direction of a field may be corrected by adding to it other fields which cancel out the undesirable component, so also may undesirable or excess curvature or flare of field be eliminated with the addition of the fields of another lead.

This is illustrated by the example in figure 4, which shows a sketch of the field of lead I before and after correction. The addition of the transverse lead made up from electrodes on the sides below the level of the heart serves to cancel out the curvature of lead I, since the field of the lower lead has the opposite curvature. It might be noted that the errors in general direction of the two leads also tend to cancel each other.

Another example is given in figure 5, which shows a central terminal chest lead before and after correction. In this case an electrode on the back was added. The excess flare toward the posterior side of the heart is cancelled out by the deficiency in the flare in the lead which is combined with the first one.

Simultaneous correction of the general direction and the curvature of the lead field within the heart, especially if the field is to be corrected at two or more points, may become rather complicated. Using the principles outlined above and a larger number of suitable leads, the desired field can be closely approximated either by a mathematical procedure or by an experimental method of successive approximations. A detailed discussion of this matter is beyond the scope of this paper.

Synthesis of Leads by Adjustment of Lead Field Current at the Body Surface

In combining leads in such a fashion that undesirable aspects of the fields cancel out, there will always remain small imperfections in the result. By combining more and more leads it may be possible to cancel out even these small imperfections until, through the use of an infinite number of leads, the resultant field becomes exactly that desired. However, when this is done, it will be found that the lead field current is passing into and out of the body through electrodes covering its entire surface. That is to say, a perfect lead requires in general a surface current "distribution" of a certain specific type. For a given lead field in the heart, then, what is this current distribution?

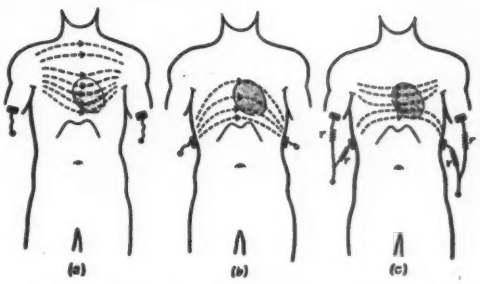

FIG. 4. Correcting the curvature of the field of lead I. (*a*) Usual lead I. (*b*) Corrective lead. (*c*) Lead I, corrected.

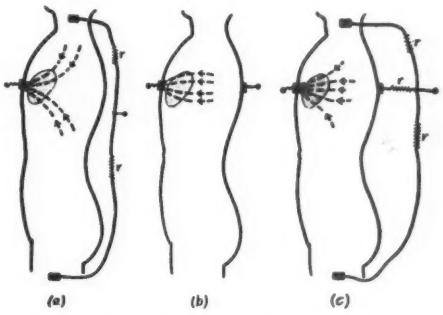

FIG. 5. Correcting the flare of a unipolar chest lead. (*a*) Usual lead. (*b*) Corrective lead. (*c*) Corrected combination.

A Simple Sagittal Lead

As an elementary and practical illustration of the idea involved here, consider the construction of a simple lead for obtaining, in the best possible manner, the sagittal component of the mean heart vector.

Looking at the body from the side, the flow lines of the field of a perfect sagittal lead should have the pattern shown in figure 6*a*. To

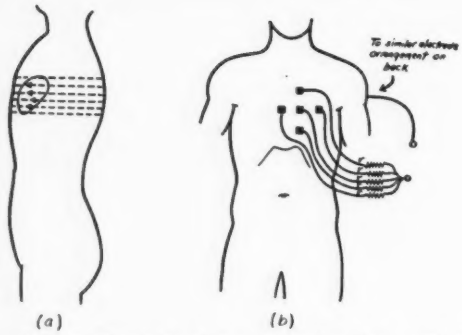

FIG. 6. Simple lead for obtaining the sagittal component of the heart vector. (*a*) Desired field. (*b*) Network yielding a close approximation to it.

obtain a lead field of this kind it is nearly self evident that a system of multiple electrodes located on the left posterior chest behind the heart through which currents enter and a similar set of electrodes on the precordium from which they pass out will be required.

Such an arrangement is shown in figure 6*b*. Here five electrodes are placed on the chest over the heart, and each of these electrodes is connected through a large resistance (for example, 20,000 ohms) to the positive terminal of the lead. The negative terminal of the lead is attached to a similar set of electrodes on the back directly behind the heart.

The positive terminal of this lead is the "*S*" terminal which was previously used, along with the *R*, *L* and *F* terminals, to produce lead fields at the heart center (fig. 3). So far as the external networks are concerned, this may be thought of as a single electrode in series with a resistor whose value is one-fifth of *r*. This resistance must be taken into account in the construction of the networks shown in figure 3.

Obviously, the greater the number of electrodes used in front of the heart, the more regular the field there will be. One way to test the accuracy of using a fairly small number of electrodes is to compare the actual electrocardiographic voltages obtained this way with the voltages obtained from a lead using a large number of electrodes.

The Homogeneous Box Model

It is possible to get insight into the surface current distributions required of perfect leads by considering a simple yet not inaccurate model of the body, a box shaped conductor of uniform conductivity. In order to agree with the average dimensions of the human torso, the box should be about half as wide and two-fifths as deep as it is long.

It is not difficult to see what the surface current distribution should be in this case when it is desirable to construct leads for determining various components of the heart vector. If a uniform amount of current enters all points on the top of this box, and leaves it at the bottom, and no current enters or leaves the sides, then it is evident from the symmetry of the situation that the field of current at all points within the box will be uniform and directed perpendicularly. This, of course, means that a lead producing such a surface current distribution on the top and bottom of the box will be sensitive to the vertical component of the heart vector.

To construct such a lead practically, one connects electrodes covering the areas where the current enters or leaves to the terminals of the leads through resistors (fig. 7*a*). As before, the resistors should be so large that the potential drop between the terminals is negligible in comparison to that across the resistors.

The other components of the heart vector are obtained in a similar manner. It might be noted that since the resistors connected to each side are alike, the potential of the terminal of the lead connected to a side will be the average of the potential of that side. Thus, we have just shown that the difference between the average potentials of two opposite sides of a homogeneous box-shaped conductor will be proportional to the components of the dipole moment of the electromotive forces perpendicular to those sides.

The proportionality factor depends upon the area of the sides through which the current is entering and leaving. If that area is small, the current density will be large, and if the area is large, the current density will be small. The fields of all three leads can be made equal in intensity by putting a shunt resistor of suitable value between the terminals of the

leads attached to the two pairs of sides having relatively small cross-sectional areas.

Leads of a similar kind may be used to obtain desired components of the mean cardiac vector if the body is assumed to be a homogeneous conductor of arbitrary shape or a conductor of irregular shape with a spherical or ellipsoidal heart of greater conductivity than other tissues. The latter corresponds closely with the situation that exists in the living human body. The procedure may be outlined as follows. First, assume that the lead field in the heart is uniform and pointed in the desired direction. Next, determine analytically what the field must be outside the heart, particularly its perpendicular component of current at the body surface. Lastly, construct a lead which introduces at every point on the body surface the same amount of current. It follows from the well known "uniqueness" theorem of electrical theory that this lead will produce the correct field in the heart.

In order to make the value of the lead field at the body surface exactly equal to the desired value, one would need an infinite number of resistors attached to an infinite number of minute electrodes covering the entire body surface. As a practical thing, this is obviously impossible, and also unnecessary. If a fairly small number of electrodes is used, there will be irregularities in the fields right at the surface, but these irregularities will all but disappear so far as the field within the heart itself is concerned. Only when the surface is very close to the heart and the amount of current entering or leaving there is fairly substantial need one be careful concerning this. (The lead for obtaining the sagittal component of the heart vector is a good example of this situation.) In other cases one can simply keep the total conductance (per unit area) of the attached resistors constant and the fields will smooth themselves out as they approach the heart. The best criterion for the number of electrodes necessary is comparison of voltages obtained with a large (and clinically impractical) number, and those obtained when a smaller number of electrodes is employed. When a small number of electrodes furnishes voltages nearly identical to those

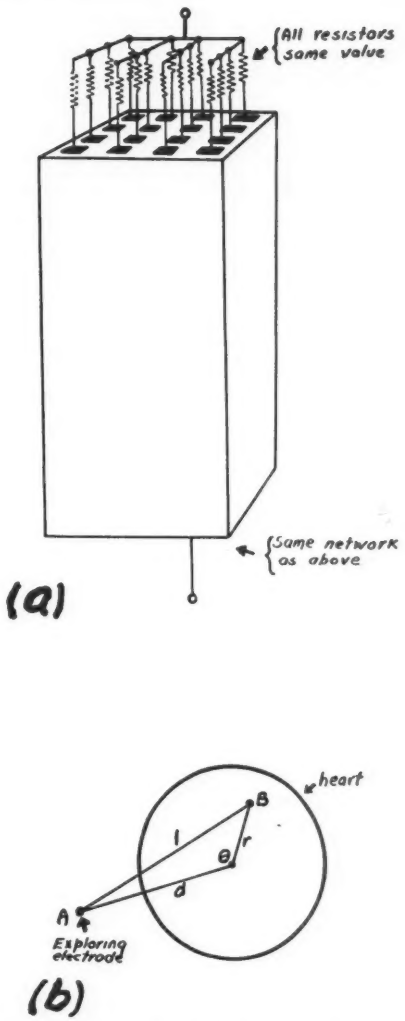

FIG. 7. (*a*) Lead for obtaining vertical component of heart vector with homogeneous box model of the body. (*b*) Diagram illustrating the calculations for the "phanton" electrode. See text.

obtained with the larger number, the smaller number will be sufficiently accurate.

Unipolar Leads

Suppose that the electromotive forces of the heart were removed from the body and placed in an infinite homogeneous conductor. They would set up an electric field producing at every point a certain potential relative to an

electrode at infinity (or an equivalent indifferent electrode). Let us now attempt to find the lead field current distribution on the body surface required of a real lead in order that it have the same potential difference induced in it.

Two different situations must be considered. In the first and simpler of the two, the exploring electrode is located on the surface of the body and is to have a lead field identical to that of an exploring electrode in a similar position in the infinite homogeneous conductor. The problem here is to obtain a satisfactory indifferent electrode. In the second case, however, the effective location of the exploring electrode is no longer restricted to the surface of body. Here a "phantom" exploring electrode is constructed which acts as if it were located at any specified point outside the heart, although all electrodes of the lead are actually located on the skin. Leads of this type might have clinical application in the location of posterior infarcts and other localized lesions.

Consider first the simpler approach, where the exploring electrode is at the body surface. If the body is assumed to be homogeneous, it is not difficult to calculate the surface current which the indifferent electrode must produce in order that the current radiate from the exploring electrode in straight lines. This is done by assuming that the radiating field already exists and determining the amount of current passing into and out of the body at all points on its surface. The procedure is similar to that used to construct heart vector leads in the case where the body was assumed to be homogeneous but of arbitrary shape.

The second case, involving the phantom electrode, makes use of the following fact. The desired field of the lead, which is based on the prototype field in the infinite homogeneous conductor, can be expressed as an infinite series, in which each term is a "spherical harmonic"; i.e., a product of a power of the distance from the center of the heart and a Legendre polynomial. For example, in figure 7*b*, if a unit current enters at A and streams out to infinity, then the potential of the lead field between B and infinity is given by

$$\phi = \tfrac{1}{4}\pi\rho l = \tfrac{1}{4}\pi\rho(r^2 + d^2 - 2rd\cos\theta)^{\frac{1}{2}} \quad (5)$$

or

$$\phi = (\tfrac{1}{4}\pi d\rho) \cdot\left[1 + \left(\frac{r}{d}\right)P_1\cos\theta + \left(\frac{r}{d}\right)^2 P_2\cos\theta + \left(\frac{r}{d}\right)^3 P_3\cos\theta + \cdots\right] \quad (6)$$

The $P_n\cos\theta$ coefficients here are the associated Legendre functions and ρ is the conductivity of the medium. This mathematical expression (6) is valid only when r, the distance from the center of the heart to the point B, where the field is measured, is less than d, the distance from the center of the heart to the location A of the exploring electrode. When r is greater than d, the sum becomes infinite.

The sum of the terms of (6) gives a simple radiating field with straight flow lines. But each term of (6) separately obeys Laplace's equation (in a homogeneous medium), and this describes a field. In order to emphasize this point, the two dimensional analogues to the second, third and fourth terms are sketched in figure 8. (The second term here is clearly the uniform field characteristic of "heart vector" leads.) Thus, the field of an exploring electrode may be thought of as the superposition of an infinite number of component fields of increasing complexity and diminishing intensity.

The values of these component fields at the body surface can be used to determine surface current distributions capable of generating each component. If the distributions associated with the first few terms of series (6) are added together, the resultant field will be the same field given by equation (6) less the field due to the sum of the terms of the series not included. Since the series is a power series which converges quite rapidly,* the effect of these neglected terms will be small, and so the synthesized field will in general be all but identical with the desired field within the heart.

* Provided that the exploring electrode is not very close to the surface of the heart.

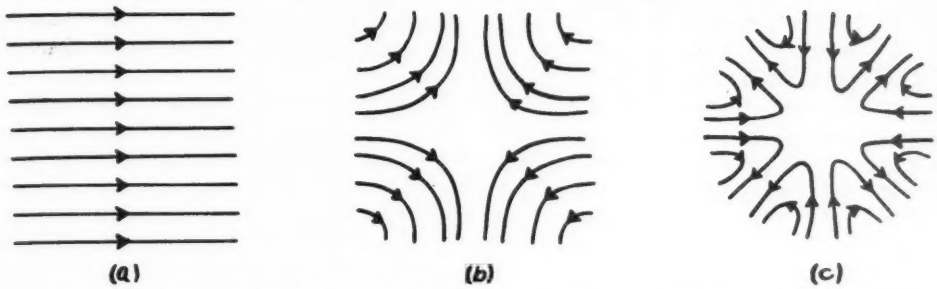

FIG. 8. Two-dimensional sketches of fields corresponding to the spherical harmonics. (*a*) (r/d) P_1 (cos θ). (*b*) (r/d)^2 P_2 (cos θ). (*c*) $(r/d)^3$ P_4 (cos θ).

Thus, in order to construct a lead where the location of the exploring electrode is to be within the body, close to the heart, the following procedure can be used: (1) Find the spherical harmonic expansion of the exploring electrode field in the heart using the infinite homogeneous conductor model. (2) Find the current distributions on the body surface capable of producing the field associated with each of the first few terms of the expansion. (3) Add these current distributions and find the resultant. (4) Construct a lead producing a surface field approximately equal to this resultant.

Of course, the close correspondence between the field of the exploring electrode in the infinite homogeneous conductor and the field in the body exists only within the "heart" region. Outside the heart, and particularly outside the circle centered on the heart and passing through the "phantom" exploring electrode, the field in the body bears no resemblance to the field which actually would be produced by a real exploring electrode at that point.

Another important fact is that, as the number of terms being used increases, the intensity of the field inside the heart, as compared to the field outside it, becomes smaller and smaller. Thus the cost of high accuracy is weak voltages. In the practical construction of leads, the noise voltages induced at the electrode surfaces and in the body tissues external to the heart might require a definite limit to the maximum number of terms which could be used.

If the heart is a sphere of higher conductivity than its surroundings, it is still possible to produce a unipolar lead type field in the heart. The reason for this is that current distributions on the surface of the body can be found which will produce spherical harmonic fields of any desired order in the sphere.* Indeed, the possibility has already been used in producing a uniform field in a more highly conducting sphere. (The uniform field is the simplest spherical harmonic.) Thus the same procedure just given for a homogeneous body can also be used here. Of course, the actual calculations will be considerably more difficult.

It might be pointed out that the relative intensities of the harmonics are not the same inside the sphere as they are outside, when its conductivity is different from that of its surroundings. In the case of the heart, which has a relatively low resistance, the high order harmonics are attenuated more than the low. This means that the heart tends to make the field within it more uniform than it would be if the heart had the same conductivity as its surroundings.

LIMITATIONS

There are two different types of limitations that arise in the design of electrocardiographic leads. These are: first, the general limitations that apply to all types of conductors, including the infinite homogeneous conductor, and second, the specific limitations which result from peculiarities in the conductivity of the body that cannot be accurately handled.

* The proof of this is quite straightforward.

The first limitation arises in the following way. Ideally, it would be desirable to know the intensity and direction of the electromotive forces at every point in the heart, or at least at a given point of interest. Unfortunately, it is not possible to design a lead whose voltage will be proportional to a certain component of the electromotive forces in a limited area of heart muscle. The reason for this is that such a lead would require that the lead field exist only in this small region and be zero elsewhere. If the electrodes of the lead are located on the body surface, they obviously cannot set up such a field.

This situation was first recognized by Helmholtz.[6] He showed that given any distribution of electromotive forces whatever in a conductor, there will always be a distribution of electromotive forces at the surface of the heart which will produce exactly the same external field. Thus the exact nature of the electromotive forces within the heart will always be indeterminate. This does not mean that it is impossible to estimate the approximate location of the electromotive forces. The probability of the lead voltage being due to an electromotive force at a certain point is proportional to the intensity of the lead field at that point. Thus, in the case of the unipolar leads taken with the exploring electrode close to the heart, it is highly probable, although not certain, that lead voltages are produced to a much greater extent by electromotive forces arising in muscle close to the electrode than in more remote regions of the heart.

The second type of limitation, which results from aberrations in the conductivity of the body tissues, comes up when one attempts to extend the procedures for synthesizing leads for a homogeneous body with a more highly conducting spherical or ellipsoidal heart to conductors having more abrupt and more frequent variations in conductivity. What happens, for example, when the heart is not a homogeneous conductor? The authors have studied a number of examples of this situation including, for example, the presence of small spherical or disk-shaped insulators within the heart. In all cases an undesirable change in the field was produced which could not be compensated for. However, large insulators were needed to produce substantial changes in the field.

The clinical electrocardiographer, however, is not interested so much in these theoretical questions as he is in how irregularities in the conductivity of the body and shape of the heart will limit the accuracy of the lead systems constructed according to the methods outlined here. It would be interesting to know how much inaccuracy will inevitably be introduced by the anisotropy of heart muscle, by the small but not negligible difference between the conductivity of heart muscle and blood, by fat pads covering areas of the heart, by a gas bubble at the top of the stomach, and similar factors. Unhappily, there is not enough data available at the moment to answer this question. There is a great deal of experimental work to be done here.

Summary

1. This paper, the last of a series of three, explains how to construct leads of any desired type. "Heart vector" and "unipolar" type leads are particularly stressed.

2. An approximate method, involving the selection and combination of leads, is given first. Some simple modifications of the standard leads and the central terminal are worked out, which would increase the accuracy of these leads when interpreted with the concepts of the Einthoven triangle and the central terminal theory of Wilson.

3. An exact method of lead synthesis is advanced next. It is illustrated qualitively with a simple lead for determining the sagittal component of the heart vector. More involved applications are then considered, which include the construction of "heart vector" and "unipolar" leads that take into account the irregular shape of the body and, to a certain extent, the variations in the conductivity within it.

4. Limitations to the synthesis of electrocardiographic leads are discussed briefly.

Acknowledgment

The authors are greatly indebted to Dr. H. C. Burger for his helpful comments and criticism on

arly drafts of each of the three papers of this eries. Many of his suggestions have been incorporated into the final manuscripts.

APPENDIX

The Lead Vector of a Tap on a Resistor

In this situation (figs. 9*a* and 9*b*) there are three electrodes, A, B and R. The R electrode is the reference electrode. The vectors $\overrightarrow{AR}$ and $\overrightarrow{BR}$ are assumed to be known. A uniform resistor, r, with a variable contact or tap is now connected to electrodes A and B, and one would like to find the lead vector, $\overrightarrow{TR}$, associated with a tap, T, on this resistor and the reference electrode R.

If a source of unit current is connected to this tap, T, and the electrode R, the current will flow through the two parts of the resistor to electrodes A and B and then back to the electrode R through the body. If the tapped resistor is very large* compared to the resistance between A and R and B and R, then the position of the tap will have the controlling influence on how the current divides. To be precise, the current flowing down the part of the resistor connected to the A electrode will be given by

$$i_A = \frac{(1/r_{TA})}{(1/r_{TA}) + (1/r_{TB})} = \frac{r_{TB}}{r_{TA} + r_{TB}} = \frac{r_{TB}}{r} \qquad (1)$$

and similarly, the current flowing down the B part of the resistor will be

$$i_B = \frac{r_{TA}}{r} \qquad (2)$$

A unit current, of course, will flow out from the reference electrode.

The electrode currents described here could have been produced in an entirely different way. Suppose that one had connected a unit source of current to AR, and $\frac{r_{TA}}{r}$ of a unit source of current to BA. Then the same current will flow through the three electrodes. This means that the lead vector associated with TR is equal to the sum of the lead vector of AR and $\frac{r_{TA}}{r}$ times the lead vector of BA. That is

$$\overrightarrow{TR} = \overrightarrow{AR} + \frac{r_{TA}}{r}\overrightarrow{BA} \qquad (3)$$

This in turn means that the tap will have a lead vector whose tip lies on the line extending from the tip of the AR lead vector to the tip of the BR lead vector at a position on the line corresponding exactly to the position of the tap on the resistor. (See fig. 9.)

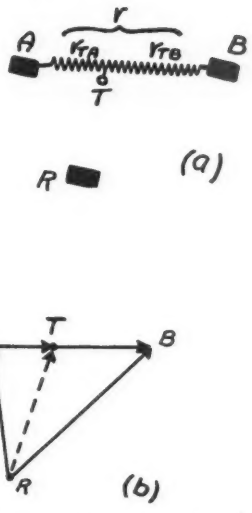

FIG. 9. (*a*) Three electrodes and tapped resistor. (*b*) Associated lead vectors. See appendix.

* It is important to realize that this resistance could be as large or larger than the input resistance of an electrocardiograph connected to T and A, without reducing the accuracy of the instrument. Of course, the electrocardiograph would have to be properly calibrated.

SUMARIO ESPAÑOL

1. Este trabajo, el ultimo de una serie de tres, explica el como construir derivaciones de cualquier tipo deseado. "Vector Cardíaco" y tipo "Unipolar" de derivaciones son particularmente enfatizados.

2. Un método aproximado, sobre la selección y la combinación de derivaciones, se describe primero. Algunas sencillas modificaciones de las derivaciones "standard" y las de terminal central se desarrollan, que podrían aumentar la precisión de estas derivaciones cuando son interpretadas por los conceptos del triángulo de Einthoven y la teoría de Wilson de terminal central.

3. Un método exacto de síntesis de derivaciones se propone después. Se ilustra qualitativamente con una derivación sencilla para la determinación del componente sagital del vector cardíaco. Aplicaciones más complicadas son luego consideradas, que incluyen la construcción del "Vector Cardíaco" y las derivaciones "Unipolares" las cuales toman en consideración la forma irregular del cuerpo y hasta cierto punto, las variaciones en conductividad dentro de este.

4. Las limitaciones en el síntesis de derivaciones electrocardiográficas se discuten brevemente.

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1853.

Surgical Treatment of Tricuspid Stenosis

By THOMAS J. E. O'NEILL, M.D., O. HENRY JANTON, M.D., AND ROBERT P. GLOVER, M.D.

In patients suffering with chronic valvular disease who are diagnosed as having mitral stenosis, there are found a few who have an associated tricuspid stenosis. The diagnosis of this combination of lesions is difficult. The unique opportunity to study the hemodynamics of "pure" tricuspid stenosis was presented when a patient, originally diagnosed as mitral stenosis, had in fact both lesions, and was treated by mitral commissurotomy. Subsequently tricuspid stenosis was suspected clinically and was demonstrated by serial catheterization studies. Tricuspid commissurotomy was performed four years after mitral commissurotomy.

TRICUSPID valvular disease in adults is usually rheumatic in origin. As seen in the mitral and aortic valves, severe anatomic distortion of the leaflets of the tricuspid valve produces insufficiency, stenosis, or an element of each. Such deformities, when slight, cause no physiologic derangements, but when marked interfere noticeably with cardiovascular function. From a clinical standpoint, the terms adynamic and dynamic tricuspid disease seem applicable.

Whereas insufficiency of the tricuspid valve may be primary when due to distorted valve leaflets, or secondary when due to changes incident to severe right heart failure, stenosis is always an organic involvement. The size of the orifice is of considerable importance in that there probably exists a critical area above which insufficiency predominates, and under which, stenosis predominates. This area has not as yet been closely defined and requires further observation.

Rarely does this disease exist as a solitary valvular defect. Reports of autopsy studies[1] demonstrate that its highest incidence is in association with both aortic and mitral disease; and its next highest incidence is in association with mitral valve involvement. A decisive clinical diagnosis usually can not be made because of the masking effects of the mitral valve lesion. Therefore, the successful surgical treatment for stenotic valvular diseases now imposes a greater demand for more accurate methods of diagnosis of stenosis of the tricuspid valve, since this lesion may no longer be regarded as having merely prognostic importance.

Operative attempts have been made simultaneously on the combination of aortic and mitral stenosis with some success, but it is apparent that both of these valves, located as they are in the left heart, render operative appraisal less difficult and intervention more feasible. The tricuspid valve being on the side opposite requires a more formidable approach for simultaneous surgery, or else necessitates a two stage operation.

The diagnosis of tricuspid stenosis is not easy to make, mainly because of the absence of unambiguous cardinal features. This problem is the greater because the principle signs and symptoms are obscured by the identical findings often seen in solitary mitral stenosis. During life, there are only two methods of differentiation available: One, elimination of the symptoms secondary to mitral stenosis by means of mitral commissurotomy, thereby allowing a residue of provocative symptoms that suggest a dynamic tricuspid stenosis. The other, by certain inductions drawn from a less than impressive set of particulars, which reflect alterations in physiology dictated by something other than mitral stenosis alone. The more important symptoms and signs suggestive of tricuspid stenosis may be listed as follows:

1. History and Cardiac Findings. The patient has auscultatory evidences of mitral stenosis associated with episodic or constant peripheral edema and/or ascites, usually never having suffered the usual pulmonary symptoms secondary to pulmonary hypertension. Such

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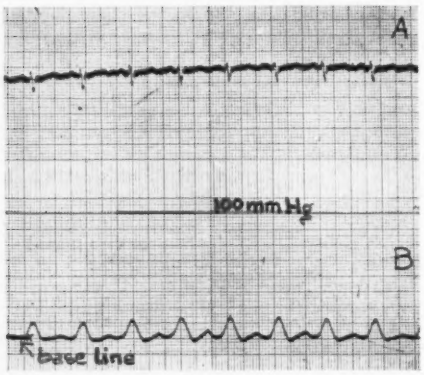

FIG. 1. (*A*) The upper tracing shows lead I of the electrocardiogram. Sinus rhythm is present. (*B*) The lower tracing was obtained with the catheter in the right atrium, recorded simultaneously with the electrocardiogram. It demonstrates a large A wave occurring at the time of atrial systole and indicates tricuspid stenosis. (Courtesy of Brith Sholom Laboratory.)

patients are not ordinarily dyspneic or orthopneic.

2. Venous Pulsations. When seen to be abnormally vigorous in the neck, these suggest tricuspid disease, regardless of whether the pulsations are caused by a regurgitation, or by atrial displacement of an otherwise flexible stenotic tricuspid valve "diaphragm." The repeated references to "liver pulsations" are possibly transmitted cardiac impulses applied to the surface of the liver itself.

3. Cyanosis. With or without jaundice, this would indicate either peripheral stasis or pulmonary stasis and could be a manifestation of mitral stenosis alone.

4. Right Atrial Enlargement. This is present in Lutembacher's syndrome and tricuspid insufficiency, as well as tricuspid stenosis. There could be absence of enlargement if the wall of the atrium is "protected" by mural thrombosis or myofibrosis.

5. Diminished Pulmonary Arterial Dimensions as Seen Radiologically. This change could occur if the tricuspid stenosis matured before the mitral stenosis.

6. Localized Diastolic Murmur at the Lower End of Sternum. There is usually great difficulty in interpreting the significance of the diastolic murmur and rarely is a diagnosis of dynamic tricuspid stenosis made on such auscultatory findings. A clear-cut demonstration, however, is helpful.

7. Catheterization. While the venous pressure is elevated and circulation times prolonged, the singular demonstration of a typical pressure tracing (fig. 1) obtained during catheterization of the right atrium is our most definitive indication of significant tricuspid stenosis. Our routine catheterizations of patients with mitral stenosis have not shown this pattern.

CASE HISTORY

The following case report represents an instance of chronic valvular disease, originally diagnosed as "pure" and solitary mitral stenosis which subsequently was found to have a residual "pure" tricuspid stenosis. Initially the mitral stenosis was eliminated by commissurotomy and after a four-year interval the tricuspid stenosis was treated with commissurotomy.

R. M., a 36 year old white woman was first admitted to the authors' service Oct. 10, 1949. At the age of 7 years the patient had had chorea which lasted for several months and was associated with frequent sore throats and nosebleeds. At age of 19 and again at the age of 22 years, joint pains and fever were present. The patient was bedfast from this time until the age of 30 years with cardiac decompensation (ankle edema, ascites, four-pillow orthopnea, dyspnea, liver enlargement, hemoptysis and showers of petechia). At the age of 33 years an episode of coma occurred which lasted for two days. An electrocardiogram obtained in 1941 showed "tachycardia" and "*no axis deviation.*" Digitalis, mercurial diuretics and a low sodium diet were utilized during the eight years prior to hospital admission.

On admission the brachial blood pressure was 140/84. There was normal sinus rhythm. A diastolic murmur was present over the apex with a sharp mitral first sound. The pulmonic second sound was accentuated. On fluoroscopy, the right ventricle and pulmonary artery were enlarged but the atria and left ventricle were not enlarged. The electrocardiogram demonstrated a rate of 105 per minute, sinus rhythm and *right axis deviation.* The P-R interval was 0.16 second. The QRS interval was 0.08 second. The RS-T segment was depressed in leads II and III. T waves were upright in II, diphasic in lead III. Cardiac catheterization findings are shown in chart 1.

Mitral commissurotomy was performed on Oct. 14, 1949. The mitral slit was found to be 20 mm. in length, and this was enlarged with the knife to a

TABLE 1.—*Cardiac Catheterizations (Patient—R. M.)*

[*Pressures in mm. Hg*]

	Right Atrium		Right Ventricle		Pulmonary Artery	
	Rest	Exercise	Rest	Exercise	Rest	Exercise
Before mitral commissurotomy—10/13/49						
Systolic / Diastolic	5 / −2 to +2		17.5 to 14 / 0 to −1		14 to 11 / 4.5 to −1	
Average	5 / 0		16 / 0		12.5 / 2	
3 months after mitral commissurotomy—1/19/50						
Systolic / Diastolic	9.3 to 7.6 / −1 to −2	14 to 10 / 0 to 0	19 to 8 / 0 to −2	20 to 17 / −3 to −7	12 to 9 / 7 to 3	21 to 17 / 8 to 3
Average	8.6 / −1.5	12 / 0	13.5 / −1	19 / −5	10 / 5	19 / 5.5
3½ years after mitral commissurotomy—5/18/53						
Systolic / Diastolic	20 to 4 / 0					
Average	12 / 0		25 / −10		14 / 6	26 / 12.5

The serial pressures illustrate several features during the three and a half year period. The pressures in the right ventricle and pulmonary artery were not elevated in spite of severe mitral stenosis and did not change significantly following the mitral commissurotomy. On the other hand, the systolic pressure in the right atrium increased remarkably and to an amplitude clearly indicating obstruction at the tricuspid valve.

length of 35 to 45 mm., with good valve function resulting. It was noted that the pulmonary artery, although enlarged to three times normal size, did not appear under increased intraluminal pressure, nor did the left atrium. Twelve days after operation the patient was discharged from the hospital in good condition.

On Jan. 17, 1950, the patient was readmitted for her three-month postoperative checkup. She was subjectively improved and had improved exercise tolerance. There was ankle swelling on one occasion. There were three or four episodes of "paroxysmal tachycardia," Each lasting about five minutes. At this examination the brachial blood pressure was 130/96. Normal sinus rhythm was present. The pulmonic second sound was accentuated. There were no systolic murmurs present. The mitral first sound was sharp and there was a diastolic murmur heard at the apex. There was no evidence of either right or left heart failure; venous pressure was not increased; the liver was not enlarged; rales were not heard at the lung bases, and no pretibial edema was present. The electrocardiogram had not changed since the previous admission. A second cardiac catheterization was performed; the results are shown in table 1.

The patient was again admitted on May 18, 1953, for a third cardiac catheterization because of symptoms suggestive of tricuspid stenosis. (See table 1.) This pressure tracing indicated the probable existence of tricuspid stenosis and operation was recommended.

On July 12, 1953, the patient was admitted for the fourth time with complaints of edema of the face, breasts and legs. One year following mitral commissurotomy, the edema of the face and breasts became evident as did a decrease in exercise tolerance. There was a history of occasional dyspnea on exertion.

On examination the face and neck were seen to be noticeably edematous. There was 1 plus ankle and pretibial edema. The liver was at the costal margin and was nontender. There was no cyanosis. Systolic pulsations were noticeable in the neck veins. The lungs were clear. The pulmonic second sound was accentuated. No longer present was the loud snap of the mitral valve. There was a diastolic rumble heard between the mitral area and the xiphoid. The electrocardiogram showed "P wave abnormality and right axis deviation."

On July 17, 1953, tricuspid commissurotomy was done, there being present a tight tricuspid stenosis. Using a mirror image technic of that used for mitral commissurotomy, the anterior commissure was opened with the guillotine knife converting an orifice measuring 13 mm. by 2 mm. to an orifice measuring 30 mm. by 10 mm. Both before and after operation there was an insignificant regurgitation present (fig. 2). Within one hour following operation most of the edema had disappeared and the patient made an uncomplicated recovery. Ten days following operation the patient was discharged from the hospital. The significant findings were as follows: The heart presented a regular rhythm; there was a very faint diastolic blow present to the left of the sternum at the fifth intercostal space; the a wave was absent in the neck veins; and there was no evidence of right heart failure.

FIG. 2. The surgical approach to the tricuspid valve in tricuspid stenosis. This procedure is precisely similar to the technic used in mitral commissurotomy but with two exceptions which are: one, the knife is carried on the left index finger instead of the right, and two, the longest presenting commissure is the one that should be cut.

At follow-up examination two and a half months after operation the following facts were established. There was no edema present; mercurial diuretics were unnecessary; there was no need for pillows while sleeping; the patient had resumed her occupation as a secretary.

Comment. Appreciating the widespread employment of commissurotomy in the treatment of mitral stenosis, we are faced with the question of how many cases have had unrecognized tricuspid stenosis of a degree serious enough to obviate a clinical cure. In view of a certain percentage of failures in otherwise adequately operated patients, attention might be directed with profit toward the possible coexistence of tricuspid stenosis. In such instances, cardiac catheterization usually will be decisive.

Table 2 indicates that the mitral valve is involved in 90 per cent of individuals dying as a result of chronic rheumatic valve disease, while the tricuspid valve is involved in 30 per cent. The mitral valve is singularly involved in 23 per cent, while there is no instance of singular involvement of the tricuspid valve. The incidence of coexistent involvement of the mitral and tricuspid valves, excluding aortic and pulmonic lesions, is 7 per cent.

Cooke and White[5] report a total of 66 cases: 59 cases of solitary mitral valve involvement, and, in addition, seven cases having combined mitral and tricuspid involvement. Of these, there were four instances of mitral stenosis

TABLE 2.

Year Reported	Authors Series	Total Autopsies with Valve Disease	Total Number with Triscupid Disease	Total Number with Mitral Disease	Number with Mitral Disesse Alone	Number with Tricuspid & Mitral Disease Alone
1924	Coombs[1]	97	35 (35%)	97 (100%)	—	12 (12%)
1925	Thayer[2]	25	10 (40%)	20 (80%)	—	—
1927	Van Glahn[3]	101	26 (26%)	57 (56%)	—	—
1935	Bland et al.[4]	100	30 (30%)	98 (98%)	23 (23%)	5 (5%)
1941	Cooke & White[5]	217	47 (22%)	206 (95%)	59 (22%)	7 (3%)
1943	Garvin[6]	119	43 (36%)	112 (93%)	28 (23%)	4 (4%)
1947	Aceves & Carral[7]	147	49 (33%)	—	—	22 (15%)
		806	240 (30%)	(90%)	(23%)	(7%)

combined exclusively with tricuspid stenosis, indicating that mitral valve disease, exclusive of aortic and pulmonic valve disease, is complicated by tricuspid stenosis in 6 per cent of the instances.

Unfortunately, none of the other series are detailed enough to allow appraisal of these relationships, and it is hoped that future reports will better illuminate this problem.

Conclusions

1. Some patients with mitral stenosis will be found to have an associated tricuspid stenosis. The incidence of this association is probably around 6 per cent.

2. A case history of one such instance is presented with surgical treatment by commissurotomies resulting in an apparent clinical cure.

3. Appreciation of certain criteria, which are discussed, together with right heart catheterization, will be an aid in the diagnosis of tricuspid stenosis.

Sumario Español

Entre los pacientes que sufren con enfermedad crónica valvular diagnosticados como estenosis mitral, hay algunos que tienen una estenosis tricúspide asociada. El diagnóstico de esta combinación de lesiones es difícil. La oportunidad singular de estudiar la hemodinámica de un caso "puro" de estenosis tricúspide se presentó cuando un paciente originalmente diagnosticado como estenosis mitral, tenía en lugar ambas lesiones y fué tratado por comisurotomía. Subsiguientemente estenosis de la tricúspide se sospechó clinicamente y se demostró por medio de estudios de cateterismo. Comisurotomía tricúspide se hizo cuatro años después de la comisurotomía mitral.

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Fatal Myocardial Sarcoidosis

A Case of Sudden Death

By J. D. Stephen, B.Sc., M.B., Ch.B.

The case history of a 47 year old white man who died suddenly is given. At autopsy extensive replacement of the myocardium by sarcoid granulation tissue was found. The lesions of sarcoidosis were also present in the lungs, the spleen, the hilar and mesenteric lymph nodes.

IN RECENT years attention has been directed to the multiplicity of organs which may be affected in sarcoidosis. Originally described as a disease of skin and lymph nodes, sarcoid is now known to be capable of producing lesions in almost all the organs of the body. In 1929 sarcoid lesions in the epicardium were described by Bernstein and his colleagues.[1] In 1937 Nickerson[2] observed a case of fulminating sarcoidosis in which involvement of the myocardium and endocardium was found at autopsy. Since then a number of other cases have been recorded and death has been attributed to the myocardial lesion in at least eight cases[3–10]; all of these occurred in Negroes, save one recorded by Yesner and Silver.[10] This report dealt with the death of a 54 year old white male which was attributed to sarcoidosis of the myocardium. The present communication records the sudden death of a white man, aged 47, as a result of extensive involvement and replacement of the myocardium by sarcoid.

Case Report

R. C., a 47 year old white male, was admitted to Regina General Hospital on Dec. 21, 1950, and discharged on Jan. 30, 1951. He complained on admission of chest pain and shortness of breath for the preceding 24 hours. He stated that on the previous day he was stricken quite suddenly with a constricting pain beneath the sternum. The pain did not radiate but maintained its severity for three hours, after which it subsided somewhat; during this time the patient sat upright in a chair. He received a hypodermic injection 18 hours after the onset of pain and this provided some relief. He stated that he suffered a similar attack in the spring of 1950 while he was driving a tractor. The pain was so severe as to cause him to fall from the vehicle.

On admission he was a mildly obese man of good stature, complaining of slight nausea. The heart rate was 160 and the beats of irregular strength; gallop rhythm was present; blood pressure was 110/80. The heart did not appear enlarged on physical examination and no murmurs were heard. The radial pulse was 80 with a tendency to alternate strong and weak beats. The lungs appeared clear. The remainder of the physical examination was unremarkable. A chest film on December 27 revealed no bony abnormalities of the thorax. The right diaphragm was considerably elevated and there were some irregular minimal streaky shadows across the right lung base. The heart shadow appeared normal. On January 26 another chest plate was made and the right diaphragm had come down nearly to normal level. The infiltration previously seen in the right base had disappeared. Some very faint infiltration was seen, however, in the outer right second and third intercostal spaces which was not present on the previous film. The cardiovascular shadow appeared to be within normal limits. The impression at that time was of a right basal lesion which had resolved with the presence now of a new lesion in the upper third of the right lung field. An electrocardiogram (fig. 1) was taken and showed evidence suggestive of myocardial and subendocardial ischemia.

The clinical impression was one of coronary thrombosis and the patient was treated with anticoagulants which were begun on December 22 and discontinued on January 15.

The hospital course was uneventful. The patient was confined to bed until January 3 at which time he was allowed bathroom privileges. He had no recurrence of his chest pain and appeared to be making satisfactory progress. On January 21 he was allowed to sit up for a short time and this privilege was gradually extended until his discharge from the hospital. At the time of his discharge he appeared to be considerably improved.

On February 9 he had some teeth extracted under anesthesia and appeared to tolerate this procedure well. On February 13 he was found dead in a hotel

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room. He had evidently died suddenly as he had been seen in apparently good health shortly before his death. His death was the subject of a coroner's investigation.

Autopsy Findings (ML-5-51): The autopsy was performed 17 hours after death. The body was that of a well nourished, middle-aged man of good nutrition. The skin surface appeared normal.

The lungs were voluminous and heavier than normal; right weighed 850 Gm., left 780 Gm. Numerous adhesions were present between the visceral and parietal pleural surfaces. On palpation the lung texture felt coarse. An extensive dissection of the bronchial system was undertaken but no evidence of primary neoplasm was found. The lungs were not conspicuously pigmented, and there was no evidence of pneumonia. Moderate pulmonary edema was present.

The heart weighed 430 Gm. The pericardial sac appeared healthy and contained 20 ml. of clear yellow fluid. Inspection of the heart before dissection revealed numerous white spots on the anterior and posterior surfaces of both ventricles and auricles. These did not have the appearance of milk spots and on section proved to be fibrous tissue. The fibrous tissue, however, appeared somewhat more granular than normal, and its distribution was quite irregular; it bore no relationship to the coronary artery system. Similar lesions were noted in the papillary muscles. The lesions encroached on the endocardial surface of the heart. The largest fibrous area was present fairly high up on the posterior wall of the left ventricle under the posterior cusp of the mitral valve, and much of the anterior wall of both right and left ventricles was replaced. The endocardium and valves themselves were unremarkable. The coronary arteries were comparatively free from atheroma. The aorta showed moderate atheroma together with some fatty streaking of the intima.

The peritoneal cavity appeared healthy. The gastrointestinal tract, liver, gallbladder and biliary passages, pancreas, adrenals, kidneys and testes all appeared healthy.

The spleen was considerably enlarged, weighing 590 Gm. Section revealed the bulk of the parenchyma to be normal in color and soft in texture. Scattered throughout, however, were several small white, firm, circumscribed nodules, the largest measuring 1.5 cm. in diameter. The texture of these nodules was indistinguishable from that of the fibrous tissue in the myocardium.

Enlargement was noted of the hilar lymph nodes and of the mesenteric lymph nodes. The texture of the nodes was soft.

The skull and brain were healthy. The pituitary was normal. X-rays of the long bones and the digits, taken at autopsy, revealed no abnormality.

Cause of Death: At autopsy the cause of death was thought to be acute heart failure resulting from extensive fibrous replacement of the myocardium.

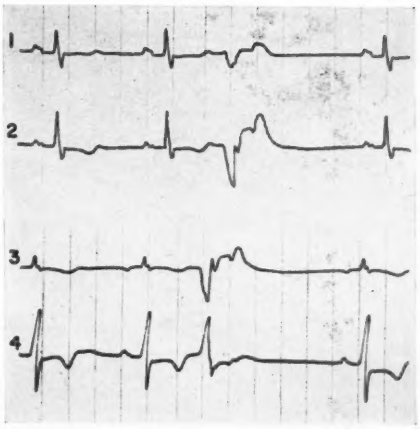

FIG. 1. The electrocardiogram

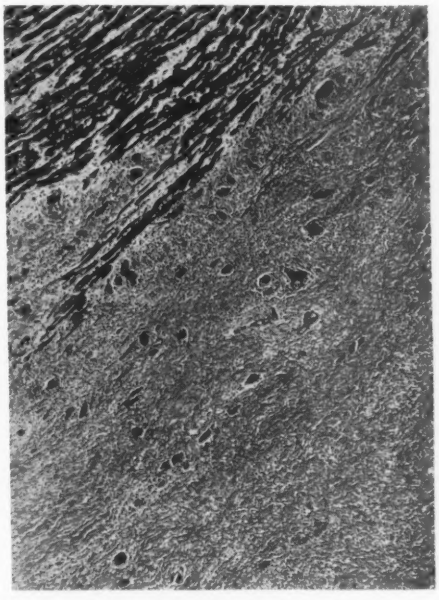

FIG. 2. A low power view of the edge of the lesion. (× 40.)

Histologic examination of the lesions in the myocardium revealed them to be areas of fibrosis in which multinucleate giant cells were abundant (figs. 2, 3 and 4). The connective tissue was sparsely infiltrated by lymphocytes but, on the whole, avascular and collagenous, and the giant cells lay scattered irregularly in it. In a few areas the giant cells lay in clumps. Some of these cells contained rounded Schaumann bodies but no asteroid inclusions were seen. In a few areas the connective tissue

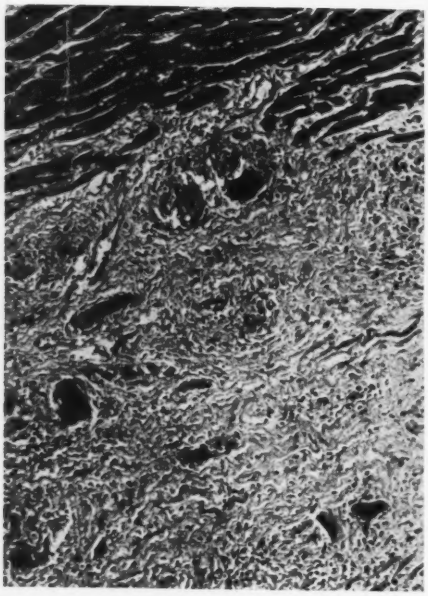

FIG. 3. The edge of the lesion showing more detail. (× 120.)

FIG. 4. A cluster of multinucleate giant cells. (× 120.)

FIG. 5. A sarcoid follicle in a lymphatic in the lung. (× 120.)

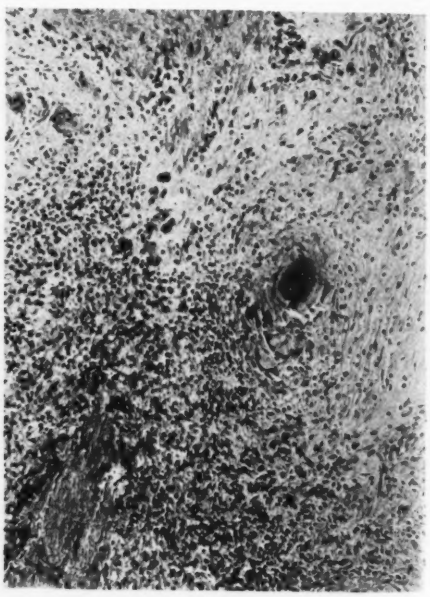

FIG. 6. A sarcoid follicle in the spleen. (× 100.)

was more cellular and showed a tendency to whorling and the formation of tubercle-like nodules, but in the myocardium these were not numerous.

The lung showed an interesting picture (fig. 5). Follicular lesions composed of endothelioid cells with numerous giant cells were present in the peribronchial and perivascular lymphatics. No gross areas of fibrosis were seen.

The spleen was congested and cellular. The sinus lining cells were more prominent than usual. The pale nodules were fibrous areas similar to those in the myocardium. In this region, however, the connective tissue was more cellular and follicles were more numerous. Giant cells were abundant (Fig. 6).

The hilar and mesenteric lymph nodes were extensively replaced by a granuloma of follicular architecture. The follicles were composed of endothelioid cells and numerous giant cells.

Histologic examination of the liver, kidney, pancreas, adrenals, thyroid and pituitary failed to reveal the presence of the characteristic follicles.

Stains for the tubercle bacillus were negative. Periodic acid Schiff stains failed to reveal any evidence of fungus. In none of the lesions was there any caseation.

The histologic picture was compatible with a diagnosis of sarcoid. It is generally agreed that the diagnosis of this disease can be made only histologically and must then fulfill certain criteria.[11]

Summary

A case is presented of a 47 year old white man who died suddenly. At autopsy, extensive replacement of the myocardium by granular fibrous tissue was found. Histologic examination of the myocardium revealed the presence of sarcoidosis. Sarcoid lesions were also present in the spleen, in the perivascular and peribronchial lymphatics of the lung and in the mesenteric and hilar lymph nodes.

Acknowledgment

I am indebted to Dr. D. E. Rodger, Regina, for access to the clinical records of this case.

The photomicrographs are the work of Mr. Harry Wood, Regina.

Sumario Español

Se informa el caso de un paciente blanco de 47 años de edad que murió subitamente. En la autopsia se encontró un reemplazo extensivo del miocardio por tejido fibroso granular. Examen histológico del miocardio reveló la presencia de sarcoide. Lesiones sarcoides también se encontraron en el vaso, en los linfáticos perivasculares y peribronquiales del pulmón y en los ganglios mesentéricos y del hilo.

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Indicator-Dilution Curves in Acyanotic Congenital Heart Disease

By James C. Broadbent and Earl H. Wood

Dye dilution and cardiac catheterization technics were used to study 36 patients with a central left-to-right shunt due to patent ductus arteriosus, atrial septal defect or ventricular septal defect. The configuration of dilution curves following injection of dye into an antecubital vein was similar in all instances. Principal abnormalities of the curve were a prolongation of its disappearance slope and a relative reduction in the peak concentration of dye. Quantitatively expressed, these abnormalities could be correlated with the magnitude of the left-to-right shunt. Curves of normal contour were observed following surgical closure of the ductus arteriosus, and in patients with isolated pulmonary stenosis.

THE dilution of an indicator substance by the blood stream during its initial passage through the central circulation proceeds in a manner determined by several hemodynamic variables. These include, among other things, the velocity, volume and pathway of the circulating blood. Stewart,[2] Hamilton and associates[3] and others[4, 5] have derived methods for determining the cardiac output and the circulating central blood volume from dye dilution curves recorded in persons with normal circulations. More recently, Nicholson and associates,[6] in a study of patients with abnormal conditions of the circulation, observed unusual and distinctive patterns of the dye curve associated with central left-to-right and right-to-left shunts and with congestive heart failure. These observations indicated that the dye dilution curve might provide information of significant clinical value in patients with suspected or demonstrated abnormalities of the central circulatory pathway.

In order to explore this possibility, a systematic study of dye dilution curves in patients with demonstrated abnormalities of the central circulatory pathway was undertaken, employing dye injection and cardiac catheterization technics. Swan and associates[7] have reported on the characteristics of the dye curve in cyanotic forms of congenital heart disease. It is the purpose of this paper to describe the significant abnormalities of the dye dilution curve observed in a study of 26 patients with a known left-to-right shunt, and to demonstrate the correlation between the magnitude of the shunt and the degree of abnormality of the dye curve.

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Methods and Materials

Indicator-dilution curves employing the blue dye T-1824 (Evans blue) were recorded in 36 patients with acyanotic congenital heart disease. There were sixteen patients with patent ductus arteriosus, six with a defect of the atrial septum, four with a ventricular septal defect and ten with isolated pulmonic stenosis. With the exception of eight patients who had patent ductus arteriosus, the diagnosis and the magnitude of the shunt were determined by cardiac catheterization performed concurrently with the dye injection procedure. Seven of the group with patent ductus arteriosus were also studied following surgical closure of the ductus.

In all instances the injection of dye was made as rapidly as possible into an antecubital or forearm vein, followed immediately by 5 cc. of isotonic saline solution, also injected very rapidly.[6] The amount of dye injected was 10 to 40 mg. in 1 to 2 cc. of a sterile aqueous solution, or approximately 0.5 mg. per kilogram of body weight. The varying concentration of dye in arterial blood following the injection was recorded simultaneously at the ear and radial artery, using a simultaneous single and

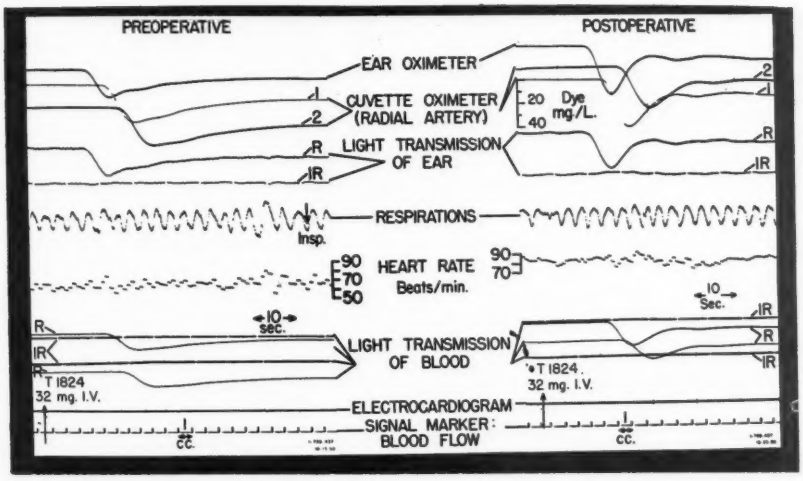

FIG. 1. Arterial dye dilution curves and other physiologic variables before and after surgical closure of a patent ductus arteriosus in a 23 year old woman (body weight: 50.0 Kg.). The dye dilution curves were recorded by means of an ear oximeter attached to the left ear and by two cuvette oximeters connected in tandem and attached to an indwelling needle in the right radial artery. The patient was breathing 100 per cent oxygen to assure constant and complete saturation of arterial blood. Simultaneous single-scale and double-scale operation of the earpiece and cuvette oximeters was used. Galvanometer traces labeled "ear oximeter" and "cuvette oximeters 1 and 2" are the single-scale recordings of the ear and cuvette oximeters, respectively. Galvanometer traces labeled "light transmission of ear" and "light transmission of blood" are the double-scale recordings, that is, the output of the respective red-sensitive and infrared-sensitive photocells, of the earpiece and cuvette oximeters. The same cuvettes were employed preoperatively and postoperatively, but their order in the tandem arrangement was reversed postoperatively. Note the prolongation of the disappearance limb and reduction in peak deflection of the dye curves recorded one day preoperatively in comparison to the curves obtained nine days after closure of the ductus.

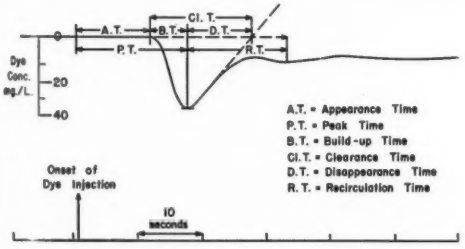

FIG. 2. Illustration of the method of measurement of the various time components ("circulation times") from a dye dilution curve. The curve is a traced reproduction of a photokymographic recording of a dilution curve recorded by cuvette oximeter from the radial artery of a normal adult male subject. The site of injection of the dye was the antecubital vein, and the amount of dye injected was 0.5 mg. of T-1824 per kilogram of body weight.

double scale ear oximeter[8, 9, 10] and a cuvette oximeter[8, 10] for whole blood, respectively. The operation of these and other instruments employed in this study was recorded continuously on 18-inch photographic paper by means of a photokymographic recording assembly described previously.[9] A typical recording is shown in figure 1.

Measurements of dye curves were made directly from the photographic record. The several time components of the curve which were measured routinely are shown in figure 2. Values for the peak of concentration of dye in whole arterial blood were determined from the curve recorded by cuvette oximeter, after the method of Nicholson and coworkers.

The technic of cardiac catheterization as performed in this laboratory and the calculations made from data so obtained have been described previously.[11, 12]

RESULTS

I. Abnormalities of Dye Curves in Central Left-to-Right Shunts

A centrally located left-to-right shunt, when of sufficient magnitude, produces an alteration in the dye dilution pattern which is highly characteristic of this circulatory disturbance

(fig. 1, "preoperative"). In its typical form, this pattern is characterized by: (1) an appearance time and a build-up time of normal duration; (2) an initial peak of concentration of dye which is lower than would be anticipated in a normal person for the amount of dye injected; (3) a prolongation of the disappearance slope of the curve; and (4) the absence of the normal secondary peak of dye concentration due to systemic recirculation of dyed blood.

One or more of these abnormal features was present in varying degree in curves from each of the 26 patients with left-to-right shunts included in this study. In some patients believed to have shunts of relatively small magnitude, the dye curve was nearly normal in configuration; in others, with evidence of a larger shunt, the curve was grossly abnormal, presenting the typical left-to-right shunt pattern. This pattern was not observed in curves from 16 normal subjects, from 10 patients with isolated pulmonary stenosis, or from seven patients with patent ductus arteriosus following surgical closure of the ductus (fig. 1, "postoperative").

Similar dilution patterns were observed in patients with patent ductus arteriosus, atrial septal defect, and ventricular septal defect. No special feature of the dye curve was observed which would permit an anatomic localization of the site of the shunt. It was of interest that the dye curve from a patient with partial anomalous pulmonary venous drainage presented the typical left-to-right shunt pattern.[13]

II. Dimensions of Dye Curves in Patients With A Central Left-to-Right Shunt

A. Time Components. Table 1 presents the average and range of values of the several time components of the dye curve recorded by

TABLE 1.—*Comparison of Average Circulation Times (in Seconds) from Dye Dilution Curves Recorded Simultaneously at Ear and Radial Artery after Injection of Evans Blue into an Antecubital Vein*

	Oximeter	Subjects	AT*	BT	DT	CLT	PT	DT/BT
Normal subjects	Ear	16	14±1† (10–27)	9±1 (6–14)	15±1 (9–26)	24±2 (15–40)	24±1 (16–35)	1.6±0.1 (1.2–2.0)
	Radial	16	15±1 (10–21)	9±1 (6–14)	14±1 (7–29)	22±2 (11–43)	23±1 (15–33)	1.6±0.1 (1.2–2.1)
Patent ductus arteriosus	Ear	16	11±1‡ (7–18)	8±1 (4–20)	22±6 (6–102)	29±7 (10–122)	19±2‡ (12–38)	2.4±0.2 (1.4–5.1)
	Radial	13	13±1 (8–21)	8±1 (4–20)	26±7 (8–99)	34±8 (12–119)	21±2 (13–41)	2.8±0.3 (1.4–4.9)
Atrial septal defect	Ear	6	10±1 (8–12)	11±2 (6–20)	48±3 (35–57)	61±5 (44–76)	22±3 (14–29)	4.8±0.7 (2.4–7.3)
	Radial	6	12±1 (8–16)	9±1 (5–14)	52±5 (38–71)	62±6 (46–85)	21±2 (13–28)	6.1±0.9 (4.5–10.2)
Ventricular septal defect	Ear	4	9±3 (4–17)	12±2 (9–16)	46±11 (27–70)	57±12 (36–86)	21±4 (14–32)	3.8±0.5 (3.0–4.6)
	Radial	3	12±4 (4–19)	11±3 (8–16)	70±28 (21–118)	80±29 (28–126)	23±7 (13–35)	7.1±3.5 (2.7–14.0)

* AT = appearance time; BT = build-up time; DT = disappearance time; CLT = clearance time; PT = peak time; DT/BT = ratio of disappearance time to build-up time; see figure 2 for diagrammatic definition of these terms.

† Figures after ± signs are standard errors of the mean. Figures in parentheses are extreme values.

‡ In 15 patients only, since moment of dye injection was not indicated in one patient.

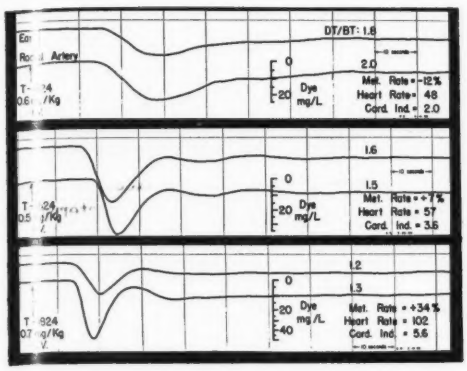

FIG. 3. Variation in the contour of dye dilution curves with physiologic status of normal subjects; dye curves simultaneously recorded from ear and radial artery in three normal adult men, ages 31 to 38 years, with individual values for metabolic rate, heart rate, and cardiac index (cardiac output in liters per minute per square meter of body surface). For the sake of clarity and simplicity these curves are traced from photographic recordings of multiple physiologic variables similar to those shown in figure 1. The cuvette oximeter (radial artery) curves were moved to the left on the record a distance equivalent to the time required for blood to flow from the radial artery to the midpoint of the cuvette. This time was calculated by dividing the volume in cubic centimeters from needle point to midcuvette by the rate of blood flow through the cuvette in cubic centimeters per second. Note that in these subjects the degree of steepness or rapidity of the dye curves apparently varies in the same direction as the cardiac output, heart rate and metabolic rate.

ear and cuvette oximeters in 16 normal subjects and in 16 patients with patent ductus arteriosus, six with atrial septal defect, and four with ventricular septal defect. The disappearance time (DT) of curves from patients with a central left-to-right shunt tends to be increased as compared with the normal average value. However, there is a considerable variability of disappearance time in normal subjects (mean 15 ± 1 seconds; range 9–26 seconds), limiting the reliability of this comparison. This variability of disappearance time in normal subjects is related in part to cardiac output, as shown in figure 3, which compares dye curves recorded from 3 of the 16 normal subjects. The disappearance time of the curve from one subject was 26 seconds when the cardiac index was 2.0 liters per minute per

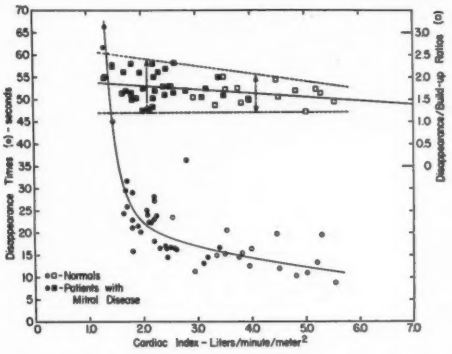

FIG. 4. Relationship of disappearance time and of ratio of disappearance time to build-up time of arterial dye dilution curves to the cardiac output in 16 normal subjects and 32 patients with mitral stenosis. The curved solid line was drawn as the visual best fit for the points (circles) representing the disappearance times. The straight solid line is the calculated linear regression line for the points (squares) representing the ratios of disappearance time to build-up time. The slope of this line (−0.085) was slightly but significantly less than zero (p value: <0.02). The double-ended dashed arrow on the left was drawn through the mean cardiac index value of the group falling below 3.0 liters per minute per square meter. This arrow covers a range of ± twice the standard deviation of the disappearance time–build up time (DT/BT) ratios of this group of subjects. The double-ended dashed arrow on the right covers a similar range for the group of subjects with cardiac indexes above 3.0 liters per minute per square meter. All injections of dye were made into a peripheral (antecubital) vein. The cardiac index values for the normal subjects were calculated from the dye dilution curves recorded from a radial artery. The cardiac indexes for the patients with mitral disease were obtained by the direct Fick method almost simultaneously with the recording of the dye dilution curves during cardiac catheterization. Note that the disappearance time–build-up time ratio values are much more nearly independent of the level of cardiac output and much less variable than are the disappearance time values for the same dye curves. The disappearance time–build-up time ratio is therefore a much more useful measurement for the detection of asymmetry in the disappearance limb of a dye curve than is the disappearance time alone.

square meter of body surface, and in another the disappearance time was 9 seconds when the cardiac index was 5.6.

This variation of the disappearance time of the dye curve with cardiac output in the absence of a shunt is better shown in figure 4.

TABLE 2.—*Relationship of Peak Concentration of Dye Curve Recorded at Radial Artery (in Milligrams per Liter of Blood)to Amount of Dye Injected (in Milligrams per Kilogram of Body Weight) in Normal Subjects and in Patients With Left-to-right Shunts*

	Amount of dye injected, mg./Kg.	Peak concentration of dilution curve, mg./L.	Ratio
	A	B	B/A
16 normal subjects	0.5±0.0* (0.4–0.7)	33±3 (21–62)	61±5 (34–103)
12 patients with patent ductus arteriosus	0.7±0.1 (0.5–1.6)	28±4 (9–50)	42±6 (18–84)
6 patients with atrial septal defect	0.6±0.0 (0.5–0.8)	16±2 (12–24)	26±3 (16–35)
3 patients with ventricular septal defect	0.7±0.1 (0.5–0.9)	17±5 (11–26)	25±6 (14–37)
4 patients after closure of a patent ductus arteriosus	0.6±0.0 (0.5–0.7)	39±7 (22–56)	63±10 (43–88)

* Figures after ± signs are standard errors of the mean. Figures in parentheses indicate the range of values.

The disappearance times of curves from 16 normal subjects and 32 patients with mitral stenosis[14] were plotted against cardiac index. In the normal subjects, cardiac output was calculated from the contour of the dye curve recorded by cuvette oximeter by the replot method of Hamilton; in patients with mitral stenosis cardiac output was calculated by the Fick method from data obtained at cardiac catheterization.

Figure 4 demonstrates that the disappearance time of the dye curve in persons without a shunt is inversely related to cardiac output, that at any level of cardiac output there is a wide range of values for the disappearance time, and that the variability of the disappearance time is greater at the lower levels of cardiac output than at the higher levels.

Thus it is apparent that the disappearance time of the curve may be increased in patients with a central left-to-right shunt, in patients with low cardiac output without a shunt, and in certain normal subjects. This fact limits the value of the disappearance time, per se, as a guide to the presence and magnitude of a central left-to-right shunt. Accordingly it became desirable to find some characteristic of the curve or an index which would be independent of cardiac output and yet permit a determination of that degree of prolongation of the disappearance slope of the curve which was due to cardiopulmonary recirculation in patients with a central left-to-right shunt.

Owing to the internal consistency of indicator-dilution curves[15] it was anticipated that variation of the disappearance time with cardiac output could be nearly eliminated if a correction was made for the steepness or the rapidity of the curve. It was found that this correction was most simply made by calculating the ratio of the disappearance time of the curve to its build-up time (DT/BT ratio). The effectiveness of this correction is shown at the top of figure 4 where the disappearance time–build-up time (DT/BT) ratio of dye curves in the same normal subjects and patients is plotted against cardiac output. Note that the disappearance time–build-up time ratio is nearly independent of cardiac output, and that at any level of cardiac output, the disappearance time–build-up time ratio is less variable than the disappearance time alone.

B. The Peak of Concentration of Dye. The peak of concentration of the dye curve recorded by cuvette oximeter was determined in 16 normal subjects and in 21 patients with a central circulatory shunt of left-to-right type. The peak of concentration was expressed as the ratio of the maximal concentration of the dye curve (in milligrams of dye per liter of whole arterial blood) to the amount of dye injected (in milligrams of dye per kilogram of body weight). Table 2 presents the average and range of values for this ratio in normal subjects and patients. A comparison of average values reveals that the peak concentration of dye curves from patients with a left-to-right shunt tends to be reduced below the normal range.

TABLE 3.—*Cardiac Catheterization and Dye Curve Data From 15 Patients with a Left-to-right Shunt Compared to Values Obtained in Normal Subjects*

Case	Diagnosis	Age, years	Sex	Cardiac output, L./min.	Cardiac index, L./min./M²	Pulmonary artery flow, L./min.	Left-to-right shunt		Data from dye curves	
							L./min.	%P.A. flow	DT/BT ratio (ear oximeter)	Maximal concentration ratio*
11	P.D.A.†	45	F	6.7	4.7	9.1	2.4	26	1.5	67.5
14	P.D.A.	16	M	7.4	3.5	10.9	3.5	32	2.2	43.6
12	P.D.A.	26	F	6.5	4.4	10.2	3.7	36	1.5	84.0
15	P.D.A.	22	F	6.1	3.6	9.9	3.8	38	2.6	34.2	
1	P.D.A.	38	M	6.6	2.9	11.2	4.6	41	3.4	29.0
9	P.D.A.	46	F	4.3	2.6	14.0	9.7	69	5.1	17.6
10	A.S.D.	45	M	4.6	2.8	6.1	1.5	25	2.4	34.6
22	A.S.D.	15	M	5.2	3.8	10.0	4.8	48	3.8	15.5
20	A.S.D.	24	M	6.7	3.9	14.1	7.4	53	6.2	31.0
18	A.S.D.	20	F	6.7	4.4	22.1	15.4	70	7.3	33.5
21	A.S.D.	24	F	4.1	2.5	15.1	11.0	73	5.0	19.0
25	V.S.D.	9	M	5.9	6.2	9.9	4.0	40	4.6	14.4
26	V.S.D.	5	F	3.3	4.6	6.0	2.7	45	3.1	‡
24	V.S.D.	18	M	4.9	3.3	9.1	4.2	46	3.0	36.5
23	V.S.D.	29	M	4.6	2.3	8.6	4.0	47	4.5	25.3
Average values in normal subjects					3.4§ (2.2–4.5)	6.7§ (4.1–8.3)	0.0	0.0	1.6‖	61.0¶

* See table 2 for exact definition.
† P.D.A. = patent ductus arteriosus; A.S.D. = atrial septal defect; V.S.D. = ventricular septal defect.
‡ Patient had dye curve recorded by ear oximeter only.
§ Average and range of values in 5 normal adult male subjects.
‖ Average values in 16 normal subjects (see table 1).
¶ Average value in 16 normal subjects (see table 2).

III. The Correlation of Dye Curve Abnormalities With Shunt Magnitude

A. The Correlation of Shunt Magnitude with Disappearance Time–Build-up Time Ratio of Dye Curve. The magnitude of the central left-to-right shunt was calculated by the Fick method from data obtained at cardiac catheterization in six patients with a patent ductus arteriosus, in five with an atrial septal defect, in four with a ventricular septal defect (table 3), and in one additional patient with partial anomalous pulmonary venous drainage. From the dye curves recorded by ear oximeter, the disappearance time–build-up time ratio was calculated and plotted against the magnitude of the left-to-right shunt, expressed as percentage of the total pulmonary arterial blood flow (fig. 5). A positive correlation was demonstrated between the magnitude of the shunt and the disappearance time–build-up time ratio of the dye curve. It is evident from this figure that the magnitude of the shunt must usually be greater than about 35 per cent of the pulmonary artery flow in order to produce a significant abnormality in this aspect of the dye curve. This conclusion is illustrated in figure 6 in which dye curves from six patients with a patent ductus arteriosus were arranged in order of increasing magnitude of the shunt. In two of three patients with patent ductus arteriosus whose shunts were 36 per cent or less of the total pulmonary arterial flow, the contour of the curve presented only minor abnormalities. However, with increasing magnitude of the shunt the contour became increasingly abnormal, with a progressive reduction in the peak of concentration of the dye curve, and an increase in the disappearance time–build-up time ratio.

B. The Correlation of Shunt Magnitude with the Peak Concentration of the Dye Curve. Dye dilution curves were recorded by cuvette (and ear) oximeter in 14 of the 16 patients who were catheterized at the time of the dye

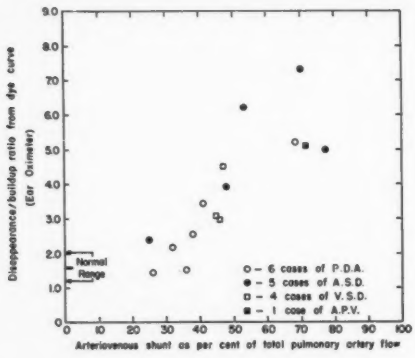
Disappearance/build-up ratio from dye curve (Ear Oximeter)
Normal Range
○ – 6 cases of P.D.A.
● – 5 cases of A.S.D.
□ – 4 cases of V.S.D.
■ – 1 case of A.P.V.
Arteriovenous shunt as per cent of total pulmonary artery flow

FIG. 5. Relation of magnitude of central left-to-right shunt to the disappearance–build-up time ratio of arterial dye dilution curves recorded by ear oximeters. All injections of dye were made into a peripheral (antecubital) vein. The magnitude of the arteriovenous shunts was determined at cardiac catheterization. The average (heavy bar) and range of the disappearance–build-up time (DT/BT) ratios obtained in 16 normal subjects are shown on the ordinate of the zero shunt line. Note that there is a positive correlation between the magnitude of the shunt and the disappearance–build-up time ratio of the dye dilution curve. However, dye curves from patients with shunts amounting to 35 per cent of the pulmonary arterial flow may have disappearance time–build-up time ratios within the range of normal subjects. P.D.A. indicates patent ductus arteriosus, A.S.D. indicates atrial septal defect, V.S.D. indicates ventricular septal defect and A.P.V. indicates anomalous pulmonary venous drainage.

injection study (table 3). In each of these 14 patients, the peak of concentration of dye was calculated from the curve recorded by cuvette oximeter and plotted against the magnitude of the left-to-right shunt, expressed as percentage of the total pulmonary arterial blood flow (fig. 7). An inverse correlation was demonstrated between the magnitude of the shunt and the peak of concentration of dye attained in these 14 patients (six with patent ductus arteriosus, five with atrial septal defect, and three with ventricular septal defect). The peak of concentration of dye was less than the lower limit of normal in seven of nine patients whose shunts were 40 per cent or more of the pulmonary arterial blood flow and was within the normal range in all of the five patients whose shunts were less than 40 per cent of the pulmonary arterial blood flow. In other words, the magnitude of the shunt was 40 per cent or more of pulmonary arterial flow before a significant reduction occurred in the peak of concentration of dye.

COMMENT

It was observed by Nicholson and associates,[6] and confirmed during this study, that dye curves are of the same general configuration (Nicholson's left-to-right shunt pattern) when patients have an atrial or ventricular septal defect, a patent ductus arteriosus, or partial anomalous pulmonary venous drainage (into the right atrium). The explanation of this phenomenon is the fact that each of these anatomic defects results in a similar functional disturbance, that is, cardiopulmonary recirculation of blood via the abnormal circulatory pathway.

A typical left-to-right shunt pattern of the dye curve has not been observed in the absence of such a shunt.* For example, this pattern was not observed in curves from seven patients following closure of a patent ductus arteriosus. Moreover, dye curves were of normal contour in 10 patients with pulmonary stenosis who had no demonstrable shunt by cardiac catheterization, and a left-to-right shunt pattern was not recorded from any of 16 normal subjects.

However, contours of dye curves which were nearly normal in their configuration have been recorded from patients with proved left-to-right shunts of relatively small magnitude. Thus, although dye curves have yielded no "false positive" results, contours representing a "false negative" result at low values of shunt have been observed. On the basis of this study in which dye was injected peripherally, it appears that the magnitude of a left-to-right shunt must be greater than about 35 per cent of the pulmonary artery flow in order to produce gross abnormality of the dye curve. A probable explanation for the apparent failure of the dye curve to detect left-to-right shunts of small magnitude is that with small shunts the

* Dye curves similar in some respects to those observed in patients with a central circulatory shunt have been recorded from patients with a peripheral arteriovenous fistula (unpublished data).

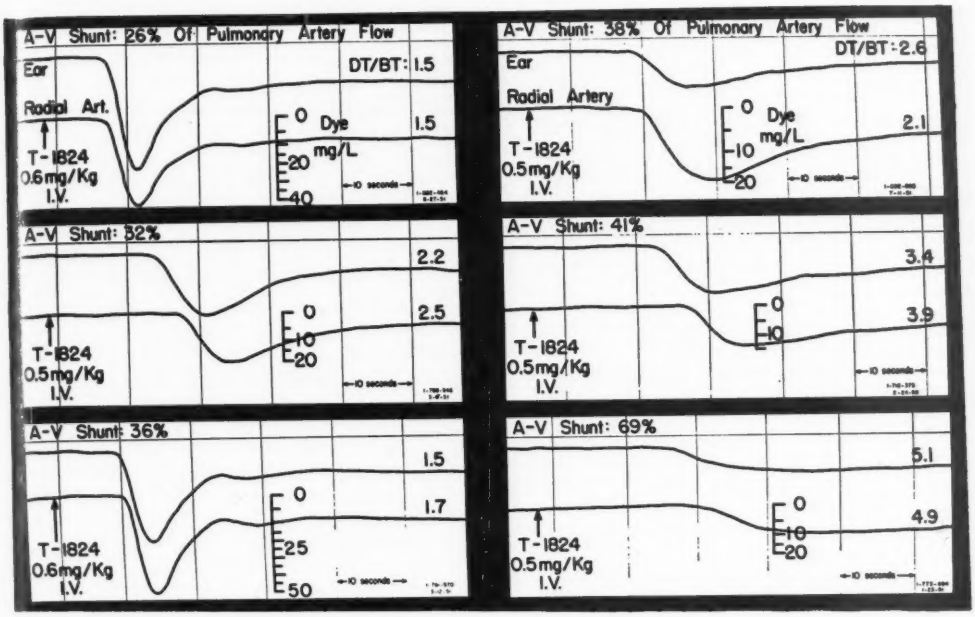

FIG. 6. Variation in the contour of dye dilution curves with magnitude of shunt in six patients with patent ductus arteriosus. The dye dilution curves were recorded simultaneously from the ear (ear oximeter) and radial artery (cuvette oximeter). They are arranged in order of increasing magnitude of the shunt. For increased clarity and simplicity these curves were traced from photokymographic records of multiple physiologic variables similar to those shown in figure 1. The time delay in the radial artery (cuvette oximeter) curve has been corrected; see legend of figure 3. Note that as the magnitude of the shunt increases from 26 to 69 per cent of the pulmonary artery flow the prolongation of the disappearance limb and decrease in peak concentration of the dye curve become evident.

percentage of injected dye recirculated is insufficient to produce an alteration of the initial rate of disappearance of dye from the heart and lungs which falls outside the range obtained in normal subjects. Recent results indicate that abnormalities in the disappearance slope are more definite for low values of shunt when central injections of dye are used.[13, 16, 17]

It has been abundantly demonstrated that the abnormalities of the dye curve which are characteristically associated with central left-to-right shunts are the result of such shunts. The alterations of circulatory dynamics produced by such a shunt, and the manner in which these alterations bring about dye curve abnormalities, can be postulated. It is well known that a central left-to-right shunt results in an increase in pulmonary blood flow; that systemic blood flow remains normal and adequate unless there is a very large pulmonary blood flow, as in certain instances of atrial septal defect; and that with large increases in pulmonary blood flow, pulmonary blood volume is increased, as indicated by the roentgenologic appearance of engorged pulmonary vessels. There may be significant enlargement of individual cardiac chambers depending on the site and magnitude of the left-to-right shunt. From a consideration of these several factors, it may be postulated that one or more of the following mechanisms may operate to produce the dye curve abnormalities characteristic of the left-to-right shunt. Prolongation of the time required for the initial passage of dye through the heart and lungs may be due to: (1) cardiopulmonary recirculation of dyed blood; (2) an increase in cardiac and pulmonary

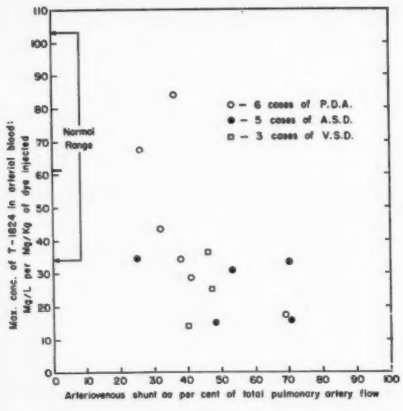
Max. conc. of T-1824 in arterial blood: Mg/L per Mg/Kg of dye injected
Normal Range
○ – 6 cases of P.D.A.
● – 5 cases of A.S.D.
□ – 3 cases of V.S.D.
Arteriovenous shunt as per cent of total pulmonary artery flow

FIG. 7. Relation of magnitude of central left-to-right shunt to peak concentration of arterial dye dilution curve. The maximal concentration of T-1824 in arterial blood was determined from the curve recorded by cuvette oximeter at the radial artery. All injections of dye were made into a peripheral (antecubital) vein. The magnitude of the arteriovenous shunt was determined at cardiac catheterization. The average (heavy bar) and range of the peak concentration obtained in 16 normal subjects are shown on the ordinate of the zero shunt line. Note that there is an inverse correlation between the magnitude of the shunt and the peak concentration of the dye dilution curve. However, dye curves from patients with shunts ranging from 20 to 45 per cent of the pulmonary blood flow may have peak concentration values within the range of normal subjects. P.D.A. indicates patent ductus arteriosus, A.S.D. indicates atrial septal defect and V.S.D. indicates ventricular septal defect.

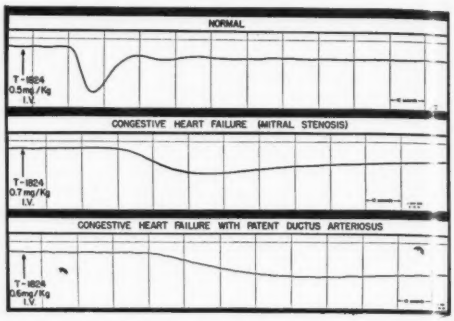

FIG. 8. Variations in contours of dye dilution curves associated with cardiac decompensation. These dye curves were recorded by ear oximeter from a normal subject and from two patients in congestive heart failure due to mitral stenosis and to patent ductus arteriosus, respectively. Note the symmetric prolongation of all components of the dye curve associated with cardiac decompensation without a cardiac shunt and the disproportionate (asymmetric) prolongation of the disappearance limb of the dye curve from the patient with decompensation and a patent ductus arteriosus. The disappearance time–build-up time ratios of these curves are as follows: normal, 1.3; mitral stenosis, 2.5; patent ductus arteriosus, 4.0.

blood volume. Reduction in the maximal concentrations of dye attained could result from: (1) the dilution of dyed venous blood with shunted but still undyed arterial blood; (2) an increase in cardiac and pulmonary blood volume.

This study has introduced the concept of the disappearance time–build-up time (DT/BT) ratio of the dye curve as an aid in demonstrating the presence or absence of a central left-to-right shunt, and as an index of the relative volume of blood flow through such a shunt, when present. Accordingly, further comments regarding this concept seem indicated.

It has been demonstrated that a prolongation of the disappearance time of the curve characterizes the left-to-right shunt pattern. However, the disappearance times of curves from certain normal subjects, and from patients with congestive failure and low cardiac output are also prolonged. Thus, the duration of the disappearance time, per se, is not a reliable indication of the presence of cardiopulmonary recirculation. Accordingly, it became desirable to find some measurement or index which would be independent of cardiac output and yet permit a determination of that degree of prolongation of the disappearance slope of the curve which is due to cardiopulmonary recirculation. It was found that dividing the disappearance time of the curve by its build-up time in effect corrects the disappearance time for the over-all degree of steepness of the curve related to the individual level of cardiac output and other factors. It has been demonstrated that (1) the disappearance time–build-up time ratio is nearly independent of cardiac output over a wide range, and (2) the disappearance time–build-up time ratio can be correlated with the magnitude of the left-to-right shunt, as determined by cardiac catheterization.

The concept of the disappearance time–build-

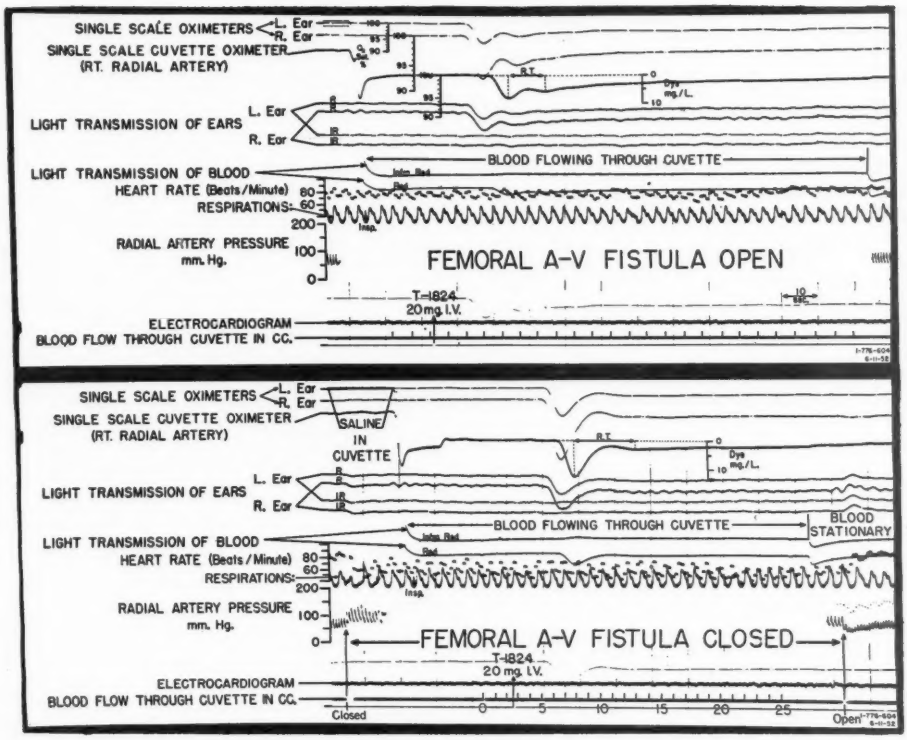

FIG. 9. Portions of the photokymographic record of arterial dye dilution curves and other physiologic variables from a boy aged 14 years, with a peripheral (femoral) arteriovenous fistula. The dye dilution curves were recorded simultaneously from both ears (ear oximeters) and the right radial artery (cuvette oximeter) when the fistula was open (top panel), and during manual occlusion of the fistula (bottom panel). The injections of dye were made into a peripheral (antecubital) vein. The patient breathed 100 per cent oxygen throughout the procedure to insure complete and constant saturation of arterial blood with oxygen. When the fistula was open, the peak of concentration of the radial dye curve was 8.8 mg. per liter, the mean systemic recirculation time (R.T.) was 10 seconds, and the cardiac output was 10.7 liters per minute per square meter of body surface. Closure of the fistula resulted in (1) a prompt and sustained increase in the levels of systolic and diastolic pressure within the right radial artery; (2) a reduction in heart rate; (3) an increase in the peak concentration of the dye curve (to 14.1 mg. per liter); (4) an increase in the mean systemic recirculation time (R.T. equals 17 seconds); and (5) a decrease in cardiac output to 8.2 liters per minute per square meter of body surface. Reopening of the fistula resulted in a lowering of radial artery pressure, and an increase in heart rate. In the top panel, the deflections of the 3 traces labeled "single scale oximeter" are calibrated in terms of percentage oxygen saturation of blood; these calibration scales reveal that the oximeter attached to the right ear was operated at a sensitivity somewhat greater than that of the other oximeters and therefore that the greater deflection of the curve recorded by this instrument is more apparent than real and not due to a greater concentration of dye in the blood of this ear.

up time ratio of the dye curve has been of considerable practical value, since it has, in many instances, permitted the distinction between normal curves of low output type, and curves associated with a central left-to-right shunt. In fact, the disappearance time–build-up time ratio was of value in recognizing the presence of a left-to-right shunt due to a patent ductus arteriosus in three patients with this anomaly who were also in congestive failure (fig. 8).

The dye injection method is of value in the differential diagnosis of acyanotic congenital heart disease since it provides a simple and

fairly reliable means of determining the presence or absence of a central circulatory shunt, of the magnitude usually associated with acyanotic congenital cardiac defects. It has been of greatest value in the study of patients with a systolic murmur in the pulmonic area, that is, in distinguishing isolated pulmonary stenosis from those forms of acyanotic congenital heart disease which are associated with a left-to-right shunt. Thus, in 10 patients with pulmonary stenosis who had no demonstrable defect of atrial or ventricular septum, the contour of the curve was entirely normal. Conversely, a completely normal contour of the dye curve was not observed in any of 26 patients with a central circulatory shunt of left-to-right type.

However, like all specialized examinations, the dye injection method is subject to certain limitations, and the interpretation of data provided by it must be integrated with other available clinical data. In particular, the dye injection method, as it is applied to the study of acyanotic congenital heart disease, is subject to the following limitations: (1) A wide variability in the contour of the curve from normal subjects makes difficult the distinction between certain normal and certain slightly abnormal contours. (2) The contour of the dye curve from patients with left-to-right central circulatory shunts of small magnitude may present only minor and perhaps hardly recognizable abnormalities. (3) It has not been possible from the contour of a peripheral dye curve to predict the anatomic location of a central circulatory shunt. Localization of shunts can frequently be accomplished by central injections of dye.[12, 15]

The following advantages of the dye injection method seem to give it a place among other laboratory technics as a valuable tool in the study of patients with acyanotic congenital heart disease: (1) in certain situations, by establishing a definite diagnosis, this method may make cardiac catheterization unnecessary; (2) the dye injection method is a safe, relatively simple technic suitable for the study of all age groups, and may even be used in those situations in which cardiac catheterization would be hazardous, or would entail the use of a general anesthetic, or perhaps would be unavailable.

Theoretic considerations, as well as our own observations and those of others,[18] indicate that dye curves in patients with a peripheral arteriovenous fistula would be similar in some respects to those recorded from patients with a patent ductus arteriosus. Thus, it was of interest to observe incidentally, in the course of this study, the configuration of the dye curves from a series of patients with femoral arteriovenous fistula. Dye dilution curves and other physiologic variables were recorded before and after temporary (manual) interruption of blood flow through the communication (fig. 9). The dye curve recorded when the fistula was open was normal except for (1) a relatively low peak of concentration of dye, and (2) an abnormally short systemic recirculation time. Closure of the fistula resulted in an increase in the peak of concentration of dye, and a prolongation of the recirculation time to the normal range.

Summary and Conclusions

1. Dye dilution curves were recorded from 16 normal subjects and from 36 patients with acyanotic congenital heart disease due to a single uncomplicated cardiac abnormality.

2. Dye curves associated with central left-to-right shunts were of similar configuration, presenting, in varying degree, two principal abnormalities of contour: (*a*) a maximal concentration of dye which was less than would be anticipated in a normal person for the amount of dye injected; and (*b*) a disproportionate increase in the disappearance time of the curve, resulting in an increase in the ratio of the disappearance time to the build-up time of the curve.

3. When quantitatively expressed, each of these abnormalities could be correlated with the magnitude of the left-to-right shunt. It was found that the magnitude of the shunt was related inversely to the peak of concentration of dye, and positively to the disappearance time–build-up time (DT/BT) ratio of dye curves in 14 and 16 patients respectively, with central left-to-right shunts.

4. Dye curves associated with central left-

to-right shunts were consistently abnormal when the magnitude of the shunt was greater than about 40 per cent of the pulmonary artery blood flow; only minimal abnormalities of contour were noted when the magnitude of the shunt was less than about 40 per cent of the pulmonary artery blood flow.

5. Abnormalities of contour specifically related to the anatomic location of a given left-to-right shunt were not observed.

6. The left-to-right shunt pattern of the dye curve was not observed in seven patients following surgical closure of a patent ductus arteriosus, in 10 patients with isolated pulmonary stenosis, or in 16 normal subjects.

Sumario Español

1. Curvas de dilución de tinte fueron registradas en 16 sujetos normales y en 26 pacientes con enfermedad cardíaca congénita acianótica producida por una sola anormalidad sin complicaciones.

2. Curvas de tinte asociadas con shunts centrales de izquierda a derecha fueron de similar configuración, presentando, en grado variable, dos principales anormalidades de contorno: (a) una concentración máxima de tinte que fué menor que lo que se anticipó en la persona normal para la cantidad de tinte inyectada; y (b) un incremento desproporcionado en el tiempo de desaparición de la curva, resultando en un incremento en la proporción de tiempo de desaparición al tiempo de formación de la curva.

3. Cuando estas anormalidades fueron expresadas cuantitativamente pudieron ser correlacionadas a la magnitud del shunt de izquierda a derecha. Se encontró que la magnitud del shunt estaba relacionada inversamente a el vértice de la concentración del tinte y positivamente al tiempo de desaparición–tiempo de formación (TD/TF) proporción curva de tinte en 14 y 16 pacientes respectivamente con shunts centrales de izquierda a derecha.

4. Curvas de tinte asociadas a shunts centrales de izquierda a derecha fueron consistentemente anormales cuando la magnitud del shunt fué mayor que 40 por ciento de la circulación en la arteria pulmonar; solamente anormalidades mínimas de contorno fueron observadas cuando la magnitud del shunt fué menos que 40 por ciento de la circulación en la arteria pulmonar.

5. Anormalidades de contorno especificamente relacionadas a la localización anatómica de un shunt de izquierda a derecha dado no fueron observadas.

6. El patrón de curva de tinte de shunts de izquierda a derecha no se observó en siete pacientes luego de cierre quirúrgico de un ducto arterioso, en 10 pacientes con estenosis pulmonar aislada, o en 16 sujetos normales.

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Role of Arterial Wall Secretion in the Regulation of Blood Pressure

By C. Jiménez Diaz, M.D., P. Barreda, M.D., A. F. Molina, M.D., and R. Alcalá, M.D.

The authors present experiments demonstrating that the hypertension produced by the stimulation of the central end of the vagus nerve is brought about by the appearance of a pressor substance in the circulating blood. The results of these experiments show that such a substance does not come from any gland nor from the central nervous system. The observed facts indicate that its origin is the arterial wall proper, from which it is directly liberated into the circulation. The pharmacologic proofs suggest that this substance is noradrenaline.

In 1947 we showed[1] that electric stimulation of the central ends of the cut vagus nerves produces a vasopressor response accompanied by release of a vasoconstrictor substance which we believed came from arterial walls. We showed subsequently[2, 3, 4, 5] that this vasoconstrictor substance does not come from an endocrine organ, and have reported our views on its origin and nature.[6] This report reviews and extends these observations.

Methods

Mongrel dogs were anesthetized with sodium pentobarbital (32 mg. per kilogram). Blood pressures were recorded on a smoked drum from a cannulated femoral artery connected to a mercury manometer. The vagus nerves were isolated in the neck and cut between ligatures; their central ends were stimulated by applying a silver electrode connected to an inductor. Duration of stimuli was between 10 and 60 seconds at a frequency of 20 to 50 cycles per second with a pulse duration of 3 to 8 milliseconds.

Results

Effect of Vagus Stimulation on Blood Pressure of Cross Transfused Animals

In 20 experiments, the cardiac ends of both carotid arteries were anastomosed to the cardiac ends of the jugular veins of another dog, and the same carotid-to-jugular anastomosis then established in the opposite direction. Thus, blood normally going to the head through the carotid arteries was carried to the right atrium of the opposite dog. Payr-cannulae were used in 10 experiments; heparin was used as an anticoagulant. To exclude the blood pressure effects of unequal exchange of blood between the dogs, a Jouvelet transfusion pump was introduced into the perfusion circuit to ensure that both venous and arterial flows were the same.

In all but two experiments, stimulation of the central cut ends of the vagus nerves of one animal caused the arterial pressure of both animals to rise, indicating release of a hypertensive substance into the blood stream which was carried to the opposite animal.

In a second group of experiments, similar carotid-jugular anastomoses were formed between two dogs and a Y tube placed in the circuits so that 40 ml. of blood could be rapidly withdrawn from or injected into either dog. Blood taken during stimulation of the vagus nerve and injected into another animal showed marked pressor activity (fig. 1, table 1).

Effect of Surgical Removal of Various Organs on the Blood Pressure Response to Stimulation of the Vagus Nerves

Stimulation of the central ends of the vagus nerves caused the usual rise in blood pressure in 6 dogs subjected to hypophysectomy, in 14 dogs after hepatectomy, in 13 after bilateral adrenalectomy, and in 11 after bilateral nephrectomy (fig. 2).

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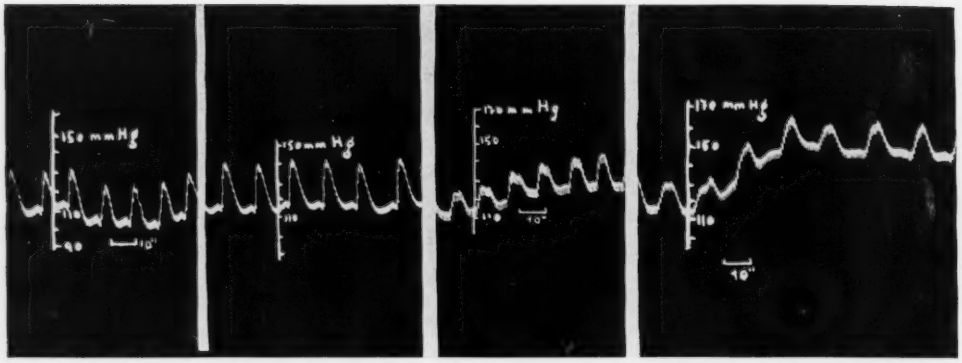


a *b* *c* *d*

FIG. 1. (*a*) Withdrawal of 40 cc. of blood from a dog, and (*b*) reinjection in the same animal. (*c*) Injection into recipient dog of 40 cc. of blood withdrawn from a dog with the vagi sectioned. (*d*) Injection in recipient dog of 40 cc. of blood withdrawn from a dog during vagi stimulation.

Effects of Vagus Stimulation in the "Split-Dog" Preparation

We have previously described a method for the vascular isolation and perfusion of the lower half of a dog's body from a reservoir or donor animal by means of a pump while the nerve supply remains largely intact. The vascular system below the origin of the renal arteries was isolated ("split-dog") by ligation of all arteries and veins below the kidneys with the exception of the external iliac arteries and veins. An iron wire tightened around the body secured the isolation. The distal end of the aorta and inferior vena cava were connected with one carotid artery and jugular vein, respectively, of a donor animal, or with a reservoir provided with an oxygenator. The distal portion of the body was then perfused by means of a pump either with blood, oxygenated plasma, saline or saline with 40 per cent red blood cells. That isolation of the two halves of the dog was relatively complete was tested by routinely injecting fluorescin or adrenaline intravenously in the two parts separately at the end of each experiment. There was no evidence of transfer of these substances from one part of the animal to the other.

TABLE 1.—*Effect on Blood Pressure of Normal Dog of Injection of 40 ml. of Venous Blood Taken before (A) and then during (B) Stimulation of the Vagus Nerves of Another Dog*

No. of Experiment	Increase in blood pressure in mm.Hg.	
	(A) Basal blood	(B) During vagus stimulation
268	0	20
269	5	32
270	10	35
271	5	20
272	10	35
301	5	21
302	27	32
303	0	34
304	5	30
305	10	65
306	10	22

The vagus nerves were stimulated in 27 such preparations; in 25 there were clear-cut rises in arterial pressure in both halves of the body though there was no mixing of blood in the two parts of the body (fig. 3).

When the lower part of the dog's body was perfused with oxygenated plasma, the effect was initially unchanged but then it rapidly disappeared. When the perfusion was made with saline solution, the vagal stimulation elicited a pressor response only in the upper but not in the lower part of the body. Our first suggestion was that the arterial wall released an enzyme capable of acting on some substrate present in the plasma. But in further experiments, on perfusing the lower half of the body with red blood cells suspended in saline solution, we found a similar pressor

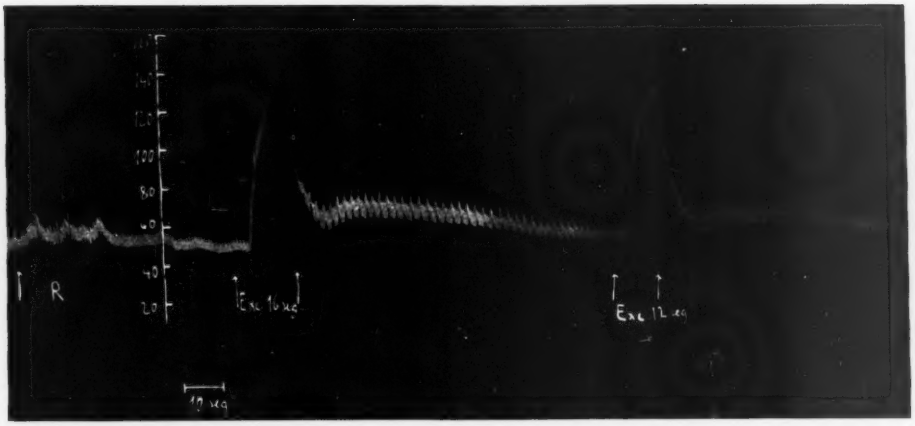


FIG. 2. Dog with the hypophysis, kidneys and adrenals removed. At Exc., stimulation of the vagi.

effect in the upper and lower half, in the same degree as when perfusion was made with oxygenated total blood. In the second place we have seen that Dibenamine (30 mg. per kilogram) abolished the pressor response caused by stimulating the vagus nerves, as well as the hypertension caused by injecting noradrenaline.

Effect of Section of the Spinal Cord on Pressor Responses to Vagus Stimulation

A segment of the spinal cord was excised at the level of the fifth cervical vertebra. Stimulation of the vagus nerves immediately and 12 hours after this procedure failed to elicit a pressor response in 50 per cent of animals. In the other half, a pressor response was present but it was greatly reduced as compared with control responses and was of a different contour.

Paper Chromatography of Extracts of Arterial Walls

Extracts of arterial walls were prepared according to the method previously described[1, 2] and were chromatographed according to a method also previously described.[9] Spots characteristic for adrenaline were more prominent than were those for noradrenaline, suggesting, as do other experiments now in progress, that adrenaline is the main pressor substance contained in arterial walls. Elution of the adrenaline and noradrenaline spots from the paper and bioassay caused typical pressor responses which were abolished or inverted by Dibenamine (fig. 4). A spot on the

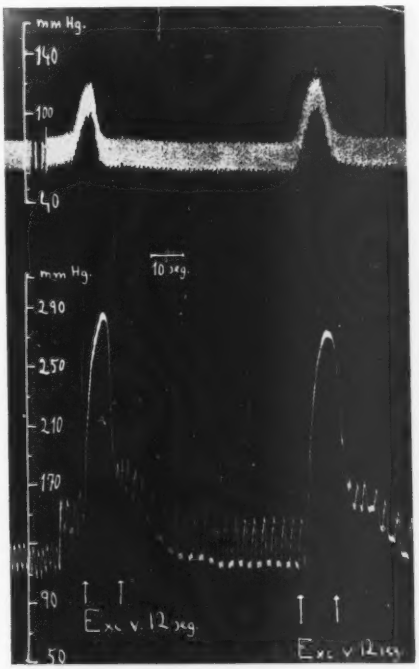
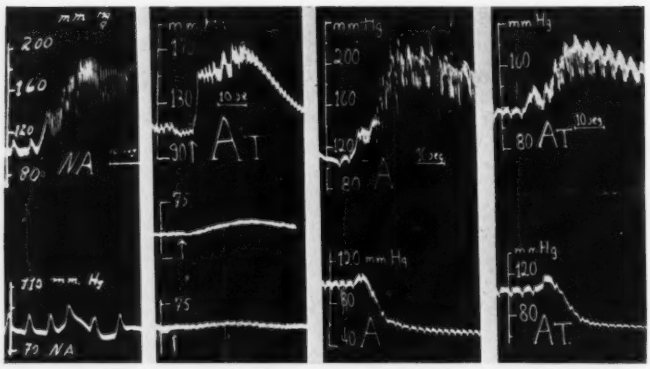


FIG. 3. Lower half of body perfused with defibrinated blood; "split dog." *Upper graph:* perfusion pressure. *Lower graph:* carotid pressure. At Exc. v., vagal stimulation.



a *b* *c* *d*

FIG. 4. *Upper graph:* responses before Dibenamine. *Lower graph:* responses after Dibenamine. (*a*) Noradrenaline, (*b*) arterial wall extract, (*c*) adrenaline and (*d*) arterial wall extract.

chromatograph just below noradrenaline caused a fall in blood pressure when it was eluted and bioassayed.

DISCUSSION

These experiments indicate that electric stimulation of the central ends of the vagus nerves causes a release of hypertensive substance which is similar in all respects to that extracted from arterial walls.

This substance is released into the blood stream, since samples of blood taken during stimulation show activity, and the hypertensive effect is transferred to another dog in cross-circulation experiments. The pressor substance in the arterial wall seems to be adrenaline and/or noradrenaline but mainly noradrenaline in circulating blood, since its activity is interfered with by administration of adrenergic blocking agents; the activity of arterial wall extracts is abolished, or reversed to a depressor effect, by these blocking agents. Paper chromatographs of arterial wall extracts revealed spots in the proper zones for adrenaline and noradrenaline, and elution and bioassay of these spots gave typical adrenaline and noradrenaline responses. There was, in addition, another spot just below those for adrenaline and noradrenaline; the identity of this substance is not known.

Release of hypertensive substances after central stimulation of the vagus nerves is probably largely from blood vessels; hepatectomy, nephrectomy or adrenalectomy did not prevent the response. Hypophysectomy also did not prevent the response and it seems apparent that the vagopituitary reflex described by Sattler[7] and Chang and co-workers, which causes the liberation of Pitressin, does not enter into the "vagal hypertension" observed in our experiments. Rather, it seems that release of pressor material from arterial walls after vagus stimulation depends upon a mechanism consisting of excitation of vasomotor centers and sympathetic outflow to the arteries.

In accord with this explanation, it was found that interruption of sympathetic outflow by section of the spinal cord at C-6 largely prevented rise in arterial pressure due to stimulation of the vagus nerves. In some experiments, however, a small rise in pressure persisted after cord section; it is likely that this effect is due to stimulation of the cervical sympathetic trunk, which lies in the vagus sheath in the dog, with release of noradrenaline from arterial walls in the head. On the other hand, these responses, which persisted after spinal cord section, might, in part, be the same as those described by Taylor, Page and Corcoran[8] who found that central vagus stimulation elicited a pressor response after cord section and after adrenergic blockade. They ascribed these responses to release by the brain of a new and unknown pressor material. While this hypothesis is attractive,

we believe that the evidence is not yet complete, and that final proof will await the clarification of certain hemodynamic, respiratory and vasomotor mechanisms that might participate. It is apparent that vagus stimulation can activate several mechanisms that modify arterial pressure. The most important of these would seem to be that one which is mediated over the sympathetic nervous system and provokes the release of pressor amines from blood vessels.

Conclusions

Electric stimulation of the central ends of the cut vagus nerves produces reflex sympathetic stimulation of the arterial walls which release pressor materials. The materials, demonstrated by paper chromatography and characterized pharmacologically, include adrenaline and noradrenaline and at least one other unknown material. It is suggested that the endocrine function of arterial walls plays an integral part in homeostasis.

Sumario Español

Los autores presentan experimentos demostrando que la hipertensión producida por el estímulo del terminal central del nervio vago se debe a la aparición de una substancia presora en la circulación sanguínea. Los resultados de estos experimentos demuestran que esta substancia no proviene de ningunal gándula o del sistema central nervioso. Los hechos observados indican que su origen es de la pared vascular propia, de donde se libera directamente a la circulación. Las pruebas farmacológicas sugieren que esta substancia es noradrenalina.

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Auricular Fibrillation and Mitral Stenosis in Bacterial Endocarditis

By JACQUES B. WALLACH, M.D., MACELLIS GLASS, B.A., LESLIE LUKASH, M.D., AND ALFRED A. ANGRIST, M.D.

The infrequent association of bacterial endocarditis with auricular fibrillation and with severe mitral stenosis is noted. The relevant literature is reviewed. Eighty-two cases of bacterial endocarditis superimposed on rheumatic heart disease and 47 examples of bacterial endocarditis without underlying rheumatic valvulitis are studied. Auricular fibrillation and severe mitral stenosis occurred less frequently in these groups than in patients with rheumatic heart disease without bacterial endocarditis. Various theories to account for these observations are analyzed and an alternative explanation is offered.

THE RARE association of auricular fibrillation and subacute bacterial endocarditis has been stressed.[1-18] This may be of diagnostic value to the clinician in differentiating rheumatic heart disease from subacute bacterial endocarditis in patients with evidence of embolization. No adequate explanation for this apparent "antagonism" has been offered. The relative infrequency of severe mitral stenosis in patients with subacute bacterial endocarditis has also been noted.[5, 6] At present no theory accounts for this relationship.

In reviewing the clinical features of subacute bacterial endocarditis, Libman,[1] in 1918, noted that "arrhythmia is remarkably infrequent." The occurrence of auricular fibrillation in reported series of cases of bacterial endocarditis since that time are summarized in table 1.

In a review of the literature, Segal[13] collected 1,351 reported cases of bacterial endocarditis; auricular fibrillation occurred in 29 (2.14 per cent). In contrast, the average incidence of auricular fibrillation in several collected series of patients with rheumatic heart disease was 48.7 per cent. However, many of the cases with alleged auricular fibrillation included in this review were inadequately reported or only casually mentioned in the original articles; the autopsy findings were usually not described. Furthermore Segal did not distinguish between patients with established auricular fibrillation who later developed subacute bacterial endocarditis (a rather rare occurrence) and those more numerous patients with subacute bacterial endocarditis who developed transient or terminal auricular fibrillation.

McDonald[18] studied seven reported series of cases of bacterial endocarditis.[2, 4, 7, 9, 10, 12, 17] Auricular fibrillation occurred in 24 (2.45 per cent) of the 980 cases reported in these seven papers but antedated the onset of the bacterial endocarditis in only two cases. In 11 instances the auricular fibrillation began after the onset of the bacterial endocarditis and in 11 other patients it was not stated which process occurred first.

These reports indicate that the development of subacute bacterial endocarditis in rheumatic patients with established auricular fibrillation is infrequent.

MATERIAL AND METHODS

In order to study this problem with a large series of uniformly examined cases, 8676 consecutive autopsies performed at the Queens General Hospital from 1936 to 1950 inclusive were reviewed. Five hundred and nine (5.9 per cent) of these were classified as rheumatic heart disease since they fulfilled criteria previously used[19]: (1) fusion and retraction of the mitral or tricuspid valves; (2) fusion and shortening of the chordae tendineae; (3) noncalcific fusion of the aortic valve; (4) any fusion, including calcific changes, of the aortic valve when it was associated with definite rheumatic

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TABLE. 1—*The Occurrence of Auricular Fibrillation in Reported Series of Bacterial Endocarditis*

Author	Total Cases	Auricular Fibrillation	Comment*
Rothschild, Sacks, Libman[2]	123	4	1 AFB terminal. 3 AFB and 1 AFL in bacteria-free stage. 1 AFB mentioned in footnote associated with Graves disease
Cotton[3]	55	1	Terminal AFB
Blumer[4]	301	4	4 AFB. 1 AFL. 9 "irregularity" without classification
Sprague[6]	20	1	AFB previously ended with quinidine. Recurred at time of infection 6 months before death
Thayer[7]	306	"5%"	4 cases of rheumatic, 1 of syphilitic heart disease. No details given
de la Chapelle, Graef[8]	—	—	1 established AFB
Fulton, Levine[9]	111	1	Terminal AFB
Laws, Levine[10]	43	2	1 transient terminal AFB (included in Fulton and Levine[9]). 1 AFB preceding bacterial endocarditis
Segal[12]	192	6	1 established AFB, 1 AFB and 1 AFL in course of bacterial endocarditis—not autopsied. 2 AFB in course of bacterial endocarditis and 1 terminal AFB with acute bacterial endocarditis autopsied
Christian[17]	150	5	3 persistent AFB. 1 transient terminal AFB. 1 transient terminal AFB in bacteria-free stage
McDonald[18]	196	21	6 AFB preceding bacterial endocarditis. 5 AFB in course of bacterial endocarditis. Both present on admission in 10 cases

* AFB = auricular fibrillation; AFL = auricular flutter.

mitral valve involvement; (5) active rheumatic heart disease with Aschoff bodies or characteristic verrucae; (6) bacterial endocarditis of the mitral or aortic valves with some evident previous distortion, but with the exact estimation of the severity of rheumatic damage being difficult. Cases showing the following changes were excluded from this study: (1) slight mitral changes (for example, tongue-like extensions of the valve cusps), or distortion which did not fulfill the criteria stated above (points 1 and 2); (2) slight aortic stenosis with or without slight mitral involvement; (3) calcific aortic stenosis with or without slight mitral changes; (4) calcification of the valve rings alone. Thus 103 cases of calcific aortic stenosis and 72 cases of doubtful origin were excluded from this study.

In the group of rheumatic hearts, bacterial endocarditis was present in 82 (16.1 per cent); in 5 of these the lesions were healed. These patients were compared with 47 instances of bacterial endocarditis in which the hearts did not meet the criteria for rheumatic heart disease described above. In each case the presence of auricular fibrillation and the severity of the mitral stenosis was noted. When the cardiac rhythm was abnormal, the time of onset relative to the beginning of the valvular infection was ascertained. The present study concerns those patients in whom auricular fibrillation preceded the development of bacterial endocarditis. The severity of the mitral stenosis was graded from 1 to 4 plus with 1 plus as the least severe involvement, yet sufficient to meet the criteria above, and 4 plus as the most severe involvement, representing valves described as "fish-mouth," "buttonhole," "slit-like," "markedly stenotic," "could not admit one finger"; 2 and 3 plus represented the intermediate degrees of severity.

In the tables the cases of "subacute" bacterial endocarditis are also listed separately from the total cases of bacterial endocarditis although the artificial nature of this distinction is appreciated.[3, 20] No significant differences between these two groups are noted.

RESULTS

There were 82 cases of bacterial endocarditis superimposed on rheumatic heart disease. Five of these were healed (all had regular rhythm) and are not included in the figures below. Of the remaining 77 cases, two patients (both with acute endocarditis) were admitted with fibrillation and the data did not indicate the length of time that this had been present; these were therefore considered with the group of established arrhythmias. Of four cases with preceding established auricular fibrillation, one patient had preceding thyrotoxicosis and two

TABLE 2.—*Occurrence of Auricular Fibrillation in All Cases of Bacterial Endocarditis Superimposed on Rheumatic and Nonrheumatic Hearts*

	Rheumatic Hearts	Nonrheumatic Hearts
Total cases of bacterial endocarditis	82	47
Healed cases	5	0
Rhythm not listed	0	2
Residual cases	77	45
Regular rhythm	62	42
Auricular fibrillation		
During infection	9 (4 acute)	1 (acute)
Present on admission	2 (2 acute)	0
Preceded infection	4 (2 acute, 1 thyrotoxic)	2 (2 terminal infection)

TABLE 3.—*Occurrence of Auricular Fibrillation in Cases of Subacute Bacterial Endocarditis Superimposed on Rheumatic and Nonrheumatic Hearts*

	Rheumatic Hearts	Nonrheumatic Hearts
Total cases of subacute bacterial endocarditis	59	7
Healed cases	4 (all RSR)	0
Rhythm not listed	0	0
Residual cases	55	7
Regular rhythm	48	7
Auricular fibrillation		
Onset during infection	5	0
Present on admission	0	0
Onset preceded infection	2 (1 thyrotoxic)	0

were examples of rather acute endocarditis. Thus only six of 77 cases (7.8 per cent) could be considered to have established auricular fibrillation prior to the onset of bacterial endocarditis and this represents a maximum estimate.

Of 47 cases of bacterial endocarditis without definite underlying rheumatic heart disease the cardiac rhythm was known in 45 patients. Forty-two (93.4 per cent) had regular rhythm, one developed auricular fibrillation in the course of acute bacterial endocarditis, and two patients with terminal bacterial endocarditis had preceding auricular fibrillation.

The figures for all cases of bacterial endo-

TABLE 4.—*Association of the Cardiac Rhythm with the Degree of Valvular Stenosis*

	Multiple Valves† All Cases of Bacterial Endocarditis 77 patients			Multiple Valves† Subacute Bacterial Endocarditis 55 patients		
Grade of Mitral Stenosis	4+	3+	1–2+	4+	3+	1–2+
Total cases	18	26	33	12	19	24
Regular rhythm	9	25	28	8	18	22
Auricular fibrillation						
During infection	6 (2*)	1	2 (1*)	3	1	1
Present on admission	1 (1*)	0	1	0	0	0
Preceding infection	2 (1*)	0	2 (1*) (1‡)	1	0	1

	Mitral Valve All Cases of Bacterial Endocarditis 71 patients			Mitral Valve Subacute Bacterial Endocarditis 49 patients		
Grade of Mitral Stenosis	4+	3+	1–2+	4+	3+	1–2+
Total cases	14	21	36	8	16	25
Regular rhythm	7	20	31	6	15	23
Auricular fibrillation						
During infection	4	1	2	1	1	1
Present on admission	1	0	1	0	0	0
Preceding infection	2	0	2 (1‡)	1	0	1 (1‡)

* Acute.

† Applies to the degree of involvement of the most severely affected valve with a superimposed bacterial infection.

‡ Thyrotoxic.

carditis are summarized in table 2. No significant differences were noted when similar comparisons were made for cases of "subacute" bacterial endocarditis only (table 3).

The type of cardiac rhythm was correlated with the degree of valvular stenosis in 77 patients with active bacterial endocarditis superimposed on rheumatic heart disease. Of 18 patients with 4 plus valvular involvement, one patient with acute endocarditis had auricular fibrillation on admission and two patients (one acute, one possibly acute) had auricular fibrillation preceding the bacterial infection. Preceding auricular fibrillation did not occur in 26 cases with 3 plus valvular involvement. Of 33 patients whose hearts showed 1 to 2 plus valvular involvement, one patient was admitted to the hospital with fibrillation and two patients had pre-existing auricular fibrillation (one was thyrotoxic and one had acute endocarditis). These cases are summarized in table 4.

These figures, though too few for statistical analysis, indicate no significant variation in the incidence of auricular fibrillation in patients with different grades of valvular stenosis. No significant difference is noted when the series is divided into groups of cases including all active bacterial endocarditis or only "subacute" bacterial endocarditis, and involvement of multiple valves or only mitral valvular involvement (table 4).

In order to determine the relationship between the severity of mitral stenosis and the development of bacterial endocarditis, the percentage of cases with varying grades of mitral valvular involvement in the group with bacterial endocarditis was compared with the whole series of patients with rheumatic heart disease. The degree of mitral valve involvement was known in 458 of the 509 cases. Two hundred ten (46 per cent) of these had severe (4 plus) mitral stenosis compared with 14 of 71 cases (19.7 per cent) with bacterial endocarditis. These results appear in table 5.

These findings indicate that bacterial endocarditis does involve valves with severe mitral stenosis, but does so less often than would be expected from the over-all frequency of severe stenosis.

TABLE 5.—*Comparison of Severity of Rheumatic Mitral Involvement in all Rheumatic Patients and in Rheumatic Patients with Superimposed Bacterial Endocarditis*

Grade of Mitral Stenosis	All Patients with Mitral Stenosis (458 cases)		Mitral Stenosis with Superimposed Bacterial Endocarditis (71 cases)		Mitral Stenosis with Superimposed Subacute Bacterial Endocarditis (49 cases)	
	No.	%	No.	%	No.	%
4+	210	46	14	20	8	16
3+	86	19	21	29	16	33
1-2+	162	35	36	51	25	51

COMMENT

The remarkable infrequency of arrhythmias in patients with subacute bacterial endocarditis was pointed out first by Libman and his associates,[1, 2] but no explanation was offered.

Levine[5] noted that a patient with evidence of mitral stenosis is distinctly less liable to develop subsequent bacterial endocarditis. He pointed out that auricular fibrillation in rheumatic heart disease is almost always associated with mitral stenosis; and in auricular fibrillation the leaflets are apt to be dense and fibrous. He suggested that the fibrous leaflets of a valve with mitral stenosis are "less fertile soil" for streptococcus viridans. The incidence of auricular fibrillation in subacute bacterial endocarditis is about 3 per cent.[13, 18] The incidence of severe (4 plus) mitral stenosis in subacute bacterial endocarditis in this study is 16 per cent. There remain then 13 per cent of the cases which do not benefit from the explanation offered by Levine. Table 4 also indicates that auricular fibrillation is associated with 1 and 2 plus mitral stenosis just as frequently as with 4 plus mitral stenosis. Furthermore the figures in tables 2 and 3 show that auricular fibrillation occurs with the same frequency in bacterial endocarditis superimposed on rheumatic as on nonrheumatic hearts. Therefore, it is not the mitral stenosis, per se, or its severity, which accounts for the low incidence of auricular fibrillation in subacute bacterial endocarditis. Segal concurs in this opinion but offered no statistical evidence.

Sprague[6] reported 20 cases of subacute bacterial endocarditis studied post mortem and

found no marked degree of mitral stenosis. He states: "It has been suggested that the rigid calcified valves of chronic mitral stenosis are less favorable ground for superimposed bacterial infection than those seen in malignant endocarditis, being subjected to less trauma since the cusps can no longer shut and so cannot strike their abnormal surfaces against one another." That some other factor in addition to less active protective antigenic agents and healing and calcification of valves is of importance is "suggested by the knowledge that this infection is much less common in childhood, at the time when rheumatic carditis is prevalent and affected mitral valves are not healed or calcified." Further it is precisely these rigid valves which Allen[15] has indicated are subject to *most* trauma since these fixed cusps meet the increased impact of the blood stream and also the more frequent and intimate contact with the bacteria in the blood. He stresses these as significant factors in the localization of bacterial endocarditis. He further emphasizes that valve cusps do not slap shut and therefore are not subject to this type of trauma in any case. Allen suggests that auricular fibrillation results in a reduction in the force of impact and of frictional resistance especially at the line of closure, with a corresponding reduction in bacterial implantation.

TABLE 6.—*Frequency of Various Grades of Rheumatic Mitral Stenosis*

Grade of Mitral Stenosis	Davis and Weiss (474 cases)		Wallach, Glass, Lukash and Angrist; 509 cases (458 were graded)	
	No.	%	No.	%
4+	57	12	210	46
3+	85	18	86	19
1–2+	332	70	162	35

Fulton and Levine[9] found that the ratio of males to females in cases of subacute bacterial endocarditis was 3:2 whereas in 762 cases of uninfected mitral stenosis the females predominated 2:1. It is this disparity which is offered to "emphasize the relative antagonism between mitral stenosis and subacute bacterial endocarditis." However, in the present study there is no appreciable difference in the frequency with which males and females were affected by bacterial endocarditis. These authors suggested that the progressive development of mitral stenosis meant continued "local allergy with persistent rheumatic state," and that, therefore, these patients have not developed the immunity requisite for subacute bacterial endocarditis.

Davis and Weiss[11] graded the degree of valvular involvement from I to IV. They found that "the distribution of the degree of rheumatic valvular damage in the 47 cases of subacute bacterial endocarditis corresponded with that for 474 cases of rheumatic heart disease, indicating that the development of subacute bacterial endocarditis is independent of the degree of underlying rheumatic endocarditis." They believed that the apparent infrequency of advanced mitral stenosis with subacute bacterial endocarditis is explained by the fact that slight lesions while just as likely to develop endocarditis "are much more common than advanced ones. The same factor is held responsible for the relatively rare occurrence of auricular fibrillation in the course of subacute bacterial endocarditis." The statistics in the present study (table 6) do not support their conclusions.

The most likely explanation for the discrepancy in the frequency of the four grades of stenosis may be the use of slightly different criteria for the selection of grade I cases. It is most probable that Davis and Weiss included many cases with minimal evidence of apparent rheumatic involvement. Their grade I "included the earliest changes, consisting in definite thickening of the free margin of the valves." Many of these may have represented commonly seen fibrous or edematous nonrheumatic thickening of the valve margins. These hearts show no definite rheumatic stigmata and have not been included in our series. This diluted the number of their cases with the most severe type of valvular distortion (4 plus).

Laws and Levine[10] also disagreed with Davis and Weiss and felt that "there is a large number of patients with persistent auricular fibrillation and valvular disease who live on

the average for several years. If the bacterial invasion of damaged valves were a mere accident, it is surprising that there are not more instances of subacute bacterial endocarditis in patients with auricular fibrillation." De Graff and Lingg[14] concluded "that patients who died of subacute bacterial endocarditis have not had rheumatic heart disease long enough to develop auricular fibrillation" which they regarded as a terminal condition.

Segal[12] pointed out that "the rare incidence of auricular fibrillation in active subacute bacterial endocarditis cannot be attributed entirely to the same incidence of severe mitral stenosis in this disease." The statistical evidence in the present study supports the views of Segal.[12] He pointed out that "the integrity of the myocardium and the underlying physiological and biological state would appear to be more closely related to the pathogenesis of auricular fibrillation than the grade of mitral stenosis per se." However, at present there is no known morphological counterpart for this "state." McDonald[13] concluded that "the answer to this problem seems to depend upon two factors which contribute to the development of auricular fibrillation: the integrity of the myocardium and the duration of the disease affecting the heart."

Each of the various theories summarized above have stressed individual factors such as the resistance of the fibrotic valve to infection, local trauma to the valve, local valve "immunity," the sex of the patient, the role of chance in valvular infection, the integrity of the myocardium, and the duration of the rheumatic valvulitis. However, an adequate overall explanation has not been offered nor have the basic mechanisms been elucidated.

It is well to define the limitations of present day knowledge. The pathology of auricular fibrillation is not known.[21] The physiologic and pharmacologic concepts of auricular fibrillation are controversial.[22] The reasons for the very frequent association of auricular fibrillation with mitral stenosis (or for that matter arteriosclerotic heart disease or thyrotoxicosis) are hypothetic. Furthermore the mechanism responsible for progressive stenosis of the rheumatic valves has not been adequately demonstrated. The relationship of such factors as the age of the patient and the duration of the valvular distortion is not well recognized. Finally, the effects of stress and the role of the adrenals have not been sufficiently studied and may play a vital part.

It has been adequately demonstrated that bacterial endocarditis represents infection of nonbacterial thrombotic lesions by organisms in the blood stream.[23] Since bacterial invasion of the blood stream occurs so frequently in all individuals,[24] it cannot be the infectious factor alone which is the significant one. Therefore the presence of rather recent nonbacterial thrombotic lesions would seem more significant for the development of bacterial endocarditis, although both are required simultaneously for the initiation of bacterial endocarditis.

It appears most probable that local and general stress represents the inciting and crucial factors responsible for the occurrence of such nonbacterial thrombotic vegetations and perhaps also for the sufficient mobilization of antibacterial forces to favor localization to the affected valve. The local stress factors determined by certain physical principles (impact and contact) have been emphasized by Allen.[15] The experimental production of nonbacterial thrombotic endocarditis in animals subjected to various stresses is now in progress. It is worth noting that one type of stress which has been successfully used is the repeated injection of killed bacteria.[25] The relationship of this technic to the statements in the older literature concerning the high degree of bacterial immunity in patients with subacute bacterial endocarditis is of interest. The stress of injections of bacteria to give this high degree of immunity may have produced the nonbacterial thrombotic lesions, thereby reproducing the above experiment.

There is a wide range of variation in the response of affected people to stress. The heart valves of the majority of individuals do not react demonstrably to the type of stress encountered in everyday life; these do not develop rheumatic heart disease. Next are the individuals who respond to some stress with the production of rheumatic valvulitis. Once

this alteration has occurred in the ground substance of the valve, future stresses may produce further changes in this collagen more readily. These changes may be manifested pathologically as nonbacterial endocarditis *in* and *on* the rheumatic valve. This nonbacterial lesion is organized, becomes incorporated as part of the valves, and is responsible for much of the valvular distortion usually attributed to the rheumatic valvulitis alone.

Considerable valvular distortion (for example, "4 plus," "fish-mouth," "button-hole") of the type frequently associated with auricular fibrillation results with the healing of repeated nonbacterial thrombotic lesions. By this stage the patient has demonstrated his ability to resist bacterial infection of his nonbacterial thrombotic lesions. These then are apt to be healed and fibrosed; hence the apparent immunity of patients with severe mitral stenosis of longer duration to subacute bacterial endocarditis. Occasionally the nonbacterial thrombotic vegetation becomes infected and bacterial endocarditis results. Similar events may occur when the basic alteration of the valve collagen is associated with sclerotic changes rather than rheumatic valvulitis. If bacterial infection of the nonbacterial thrombotic lesion occurred, the patient usually succumbed and therefore did not have time to develop progressive valvular distortion or auricular fibrillation. Likewise those rheumatic patients who died earlier in their disease of other complications (for example, embolization) could not go on to develop the more severe valvular distortion or bacterial infection. This aspect is in basic agreement with the conclusions of DeGraff and Lingg[14] and McDonald.[18]

Although auricular fibrillation occurs most frequently in association with such factors as increasing age of the patient, longer duration and greater severity of the valvular lesion, it is well to recognize that fibrillation is dependent on muscle rather than valve function. The myocardial changes in chronic rheumatic heart disease are only secondarily related to the valvular distortions. However, aging of the myocardium (presbycardia[26]) may play an additional important role similar to that which occurs in arteriosclerotic heart disease.

The exceptions to the above generalizations result from those occasional patients who continue to respond to stress with the development of rheumatic or nonbacterial thrombotic formation although the valve is markedly distorted already. Those which became infected represent the examples of bacterial endocarditis with preceding auricular fibrillation presented earlier in the paper.

Summary and Conclusions

The infrequent occurrence of auricular fibrillation and the degree of severity of rheumatic mitral valvular involvement is reported in a group of autopsied patients with bacterial endocarditis.

The unusual coincidence of bacterial endocarditis with auricular fibrillation and mitral stenosis in other series of cases is reviewed.

Previous theories for the rarity of these associations are analyzed and an alternative explanation is offered.

Sumario Español

Se informa la ocurrencia infrequente de fibrilación auricular y el grado de severidad de envolvimiento reumático de la válvula mitral en un grupo de pacientes con endocarditis bacterial a quienes se les hizo autopsia.

La coincidencia poco usual de endocarditis bacterial con fibrilación auricular y estenosis mitral en otra serie de casos se revisa.

Teorías previas para la rareza de estas combinaciones se analizan y una explicación alternativa se ofrece.

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A Morphologic Study of Canine Hearts Subjected to Fibrillation, Electrical Defibrillation and Manual Compression

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The pathologic effects on the heart of fibrillation, countershock and manual compression have been studied in canine hearts. Survival experiments have permitted evaluation of the permanence of the damage produced. Massage of the normally beating heart produced minimal nonspecific damage. Manual compression on the fibrillating heart was seen to elicit changes more severe than those observed after fibrillation alone, including occasional focal myocardial necrosis. Alternating-current countershock produced both epicardial and myocardial damage at the site of application of the electrodes. In view of their localization, these changes would not be expected to alter cardiac function appreciably. Comparable changes, but less severe in type, were found in the hearts of animals subjected to condensor discharge countershock. Padding of the electrodes with saline-soaked gauze did not appear to influence the degree of damage.

THE application of electrical currents to the heart in order to stop ventricular fibrillation has been studied by several investigators.[2, 5, 6] A number of reports have appeared describing alternating current devices for defibrillation of the human heart in the operating room,[1, 3, 4] and at least two such machines are commercially available. Although electrical defibrillation has been employed clinically, the damage which may result from this procedure has not been assayed.

The opportunity to examine the hearts of animals subjected to ventricular fibrillation, countershock defibrillation and rhythmic manual compression has been afforded by experiments on cardiac resuscitation carried on by Lape and Maison.[5] Gross and microscopic examination of such organs is important, first, to demonstrate whether or not countershock and resuscitation are productive of visible changes, and second, to establish the type of procedure which will allow the optimum resuscitative result with the least damage to the heart.

In the present study the morphologic changes in the hearts of dogs resulting from ventricular fibrillation, defibrillation by alternating current or condenser discharge countershock,* and manual compression are presented and discussed.

METHOD

In order to separate, insofar as possible, the different factors in the sequence of experimental events, fibrillation, defibrillation, manual compression and excision of the heart and to demonstrate the individual significance of each, several series of animal studies were carried out. They included: (1) basic control experiments involving the examination of hearts excised from animals at the termination of unrelated experiments; (2) fibrillation control experiments; (3) experiments on the effects of manual compression on both fibrillating and normally beating hearts; (4) alternating current countershock defibrillation studies; and (5) condenser discharge countershock defibrillation studies.

In the animals of groups 3, 4, and 5 varying periods of survival were allowed in order to obtain information regarding the restoration of normal structure. Ether anesthesia was used except in the animals of group 1 which received injections of veratrum viride where pentobarbital was used.

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* The devices used for alternating current and condenser discharge countershock are described elsewhere.[5]

Intravenous pentobarbital was also used to kill the animals in which survival had been permitted, before excision of the hearts.

After excision, the hearts were placed in a 10 per cent solution of formaldehyde in isotonic saline. Following gross examination of each heart, several blocks of the myocardial tissue were cut, imbedded in paraffin, sectioned at different levels and stained with hematoxylin and eosin.

Results

The hearts from control animals subjected to unrelated procedures showed minimal pathologic changes. Among four hearts from dogs in which extracts of veratrum viride had been injected intravenously during pentobarbital anesthesia, three showed no apparent damage either grossly or microscopically. The fourth showed epicardial venous congestion and focal red blood cell extravasation on microscopic section. No changes were found in three animals subjected to thoracotomy during ether anesthesia; a fourth revealed marked vascular congestion of the myocardium microscopically. The hearts from five dogs in which fatal anemic hypoxia was produced by severing major arteries were unremarkable in three cases; while one showed granulomatous foci and eosinophil infiltration suggesting incidental parasitic infestation, and one showed some vacuolization of muscle fibers. Except for the incidental observation of granulomatous foci in the one heart, changes found in this series may be regarded as agonal. Congestion was seen in 2 of 13 hearts.

The pathologic effects of ventricular fibrillation during ether anesthesia were studied in 16 dogs. After plane 2 surgical anesthesia was obtained, the chests of these animals were opened at the fourth left intercostal space and ventricular fibrillation was produced by stimulating the ventricles with 4 volts alternating current through the intact pericardium. In four animals the state of fibrillation was allowed to persist for one minute; at the end of this interval the heart was quickly excised. Periods of fibrillation of 2, 5, 10 and 20 minutes were permitted in three animals each. Gross inspection of these hearts revealed no abnormalities, while microscopic damage was found in nine cases. The pathologic findings consisted chiefly in fragmentation of muscle fibers, engorgement of blood vessels and disseminated microscopic hemorrhages. These changes were present both at the area of application of the fibrillating shock and at distant sites in varying degree. In seven hearts no morphologic changes were found, and the presence of calcified granulomata in one was incidental. The changes were absent or minimal in animals which were sacrificed after five minutes or less of fibrillation, while the hearts in which fibrillation had persisted for 10 or 20 minutes uniformly showed more pronounced changes. In the hearts of two of the animals subjected to 20-minute experiments subepicardial necrosis of muscle and fat was also seen. The fact that the severity of change increased in relation to the duration of fibrillation leaves little doubt that fibrillation itself, and/or the accompanying hypoxia, was responsible for the congestion, hemorrhage, muscle fragmentation and focal subepicardial necrosis.

Since in the experiments involving defibrillation and resuscitation repetitive manual cardiac compression at a rate of 25 to 35 compressions per minute was uniformly applied, the effects of compression by itself, and superimposed on ventricular fibrillation, were studied in 13 animals. In four dogs, fibrillation was induced, artificial respiration was instituted, and manual compression was applied for three minutes. Two of the hearts revealed no morphologic change; a third showed vascular engorgement and disseminated focal hemorrhages; and the fourth displayed subepicardial muscle necrosis. Four hearts were subjected to manual compression for three minutes after ether anesthesia was deepened to a fatal level. In two of these no change was observed; while focal subepicardial and myocardial hemorrhages were present in one, and focal myocardial hemorrhage and necrosis were observed in another. In addition manual compression and artificial respiration were carried out for a period of 10 minutes on five normally beating hearts; three of the hearts were excised immediately following the procedure, while two were excised after the animals had subsequently survived for a period

of two weeks. The normally beating hearts which were excised immediately after compression revealed minimal damage consisting in slight fragmentation of muscle fibers; occasional fragmentation of muscle was observed also in the hearts of the surviving animals indicating that this change was not related to compression itself.

The effects of alternating current countershock defibrillation and subsequent resuscitative procedures were studied in 18 dogs. Fibrillation was induced and allowed to persist for two minutes, manual compression and artificial respiration were then carried out for a period of three minutes. Several alternating current volleys* were then applied. Compression was resumed following these volleys. If an orderly heart beat did not return, further countershock was employed. These procedures were repeated as necessary until defibrillation and restoration of cardiac function were obtained. The range of alternating current voltage was 100 to 300 volts applied by means of self-retaining electrodes with stainless steel plates 35 to 47 mm. in diameter.[5] In some instances the electrode surfaces were covered by saline-soaked gauze pads while in others the bare metal electrodes were used. The total time of fibrillation and compression and the number of countershock volleys required for restoration of cardiac function varied widely. Fibrillation time varied from 5 to 30 minutes; the number of countershock volleys ranged from one to as many as 65. Eleven animals survived from 1 to 15 days following the experiment,† six of the dogs survived less than 24 hours, and one was not defibrillated. In spite of the wide variation in the experimental procedures, all the animals in this group showed a grossly detectable burn at the site of electrode application and various degrees of microscopic morphologic cardiac change which fell into two principal categories: (a) vascular disorders, and (b) regressive changes in muscle fibers accompanied by reactive phenomena. These changes varied quantitatively according to length of survival of the animals.

The vascular disorders were observed in the animals which died, or were sacrificed, early in the experiment. These changes were seen both at the area of application of the electrodes and at distant areas. They consisted in diffuse vascular engorgement, focal perivascular hemorrhage, and edema extending among the muscle fibers. This alteration, with variation in intensity, was quite similar to that seen in the animals in which ventricular fibrillation was the essential experimental procedure.

In contrast to the vascular disorders which were diffuse, the regressive changes and associated reactive phenomena were localized at and near the area of application of the electrodes. Both epicardium and myocardium were involved. The epicardial changes consisted chiefly in the loss of cellular lining from the serosal surface, often accompanied by subepicardial fat necrosis. Fibrinous hemorrhagic exudate with widespread granulocyte infiltration was present in one animal which died three hours after defibrillation, while in animals which were sacrificed later in the experiment fibroblastic tissue proliferation, progressively poorer in cells and richer in fibers, became apparent. Changes in the underlying myocardium extended to a depth of 2 to 3 mm. and were characterized by vacuolization of muscle fibers with frequent loss of striations and outlines and fusion of adjacent fibers into blocks of amorphous eosinophilic material as a result of necrosis. There was concurrent inflammatory reaction with a predominance of polymorphonuclear leukocytes in the early phases of the process and of connective tissue cells and fibers in the later stages. The cardiac tissue change was fundamentally the same regardless of the type of electrode used. The formation of pericardial adhesions at the area of electrode application and a moderate degree of superficial myocardial fibrosis are the expected end results of this damage; but these changes were not sufficiently extensive to warrant the anticipation of appreciable alteration of cardiac function.

Defibrillation by the application of con-

* By "volley" is meant a stimulus consisting of a series of spikes.

† These animals were sacrificed intentionally at the end of the survival period.

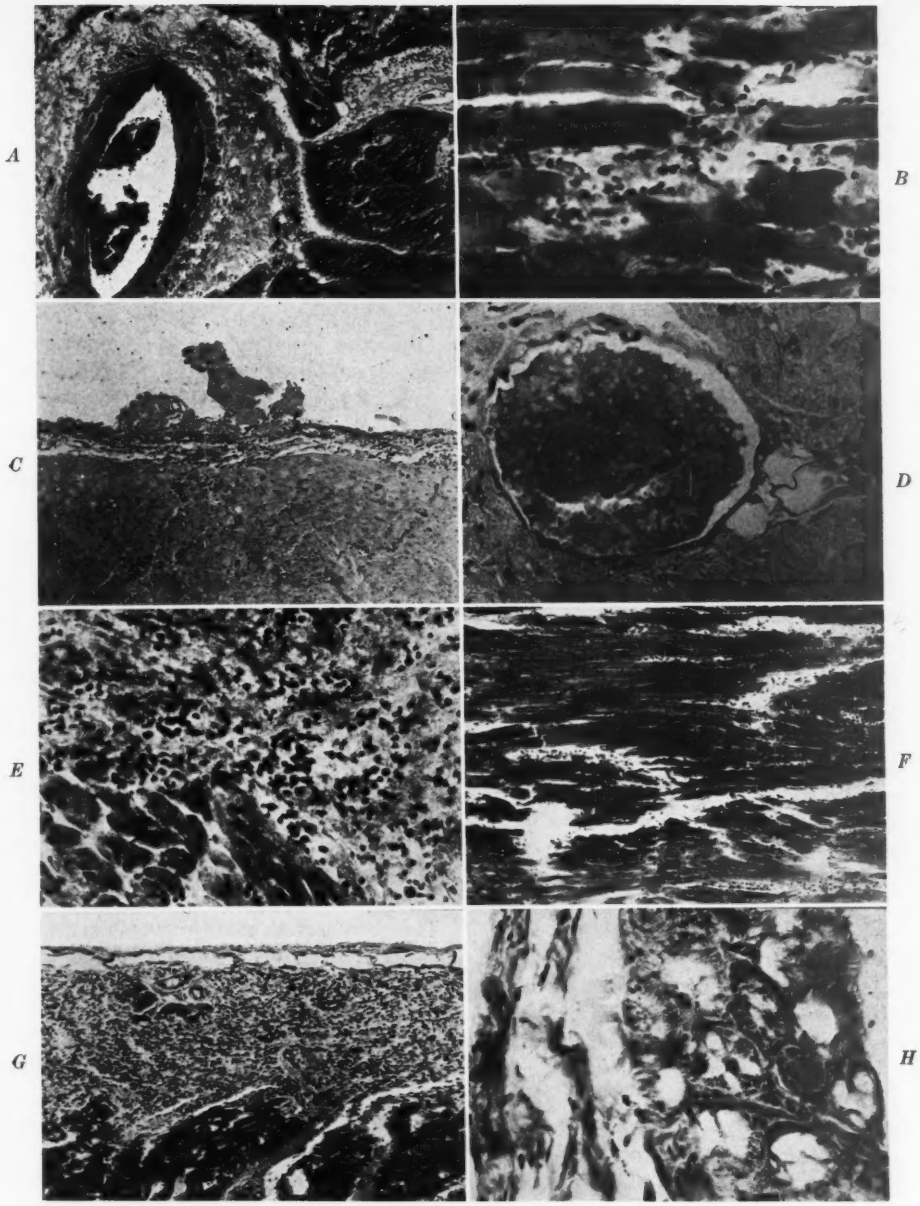

FIG. 1. (*A*) Perivascular edema extending between muscle fibers, from an animal subjected to fifty 300-volt alternating current volleys. Defibrillation was not achieved. (*B*) Fragmentation of muscle fibers, minimal granulocytic cell infiltration and tissue edema, from an animal which was defibrillated by ten 250-volt alternating current volleys. The dog survived for 12 hours. (*C*) Fibrinous epicarditis with moderate granulocyte infiltration, from a heart subjected to one 300-volt alternating current volley. The animal survived for one day. (*D*) Early thrombus in a subepicardial vein. Defibrillation was accomplished with one alternating current volley. The animal survived one day. (*E*) Interstitial myocardial edema and granulocyte infiltration in an area of muscle necrosis. The animal received thirty alternating current volleys at 300 volts and survived two days. (*F*) Focal myocardial necrosis with calcification and inflammatory reaction. Defibrillation resulted after ten 100-volt alternating current volleys; three and one half days of survival were allowed. (*G*) Epicardial fibroblastic proliferation extending into the myocardium which shows necrosis, interstitial edema and hemorrhage; from an animal which survived for five days after defibrillation by ten alternating current volleys at 300 volts. (*H*) Subepicardial fat necrosis with mesenchymal cell infiltration. The heart was defibrillated by a single 300-volt alternating current volley and the animal was sacrificed at 15 days.

denser-discharge countershock was carried out in the same way as by the alternating current countershock. It should be noted, however, that the condenser-discharge shock is a single spike in contrast to the alternating current volley which is a series of spikes. Twenty-two animals were included in the studies of condenser-discharge countershock. Defibrillation was accomplished 6 to 34 minutes after fibrillation was induced. From 1 to 14 condenser discharges at 1500 volts were required to restore an orderly heart beat. Unpadded electrodes were used in this series of animals. The survival period varied from 12 hours to 6 days, most of the animals being sacrificed at the second or third day. In contrast to the hearts of animals in which alternating current countershock was used, only one heart of the dogs which received condenser-discharge countershock revealed a grossly detectable burn. Epicardial and myocardial damage were seen, however, in microscopic sections. The damage, once more, may be placed in two classes, vascular disorders and regressive changes. The former again were characteristically diffuse, consisting in dilatation and engorgement of blood channels, perivascular edema and hemorrhage; these changes were seen in the animals which died within 24 hours after defibrillation. In one instance early thrombosis of a middle-sized epicardial vein was observed, and in five hearts recent thrombi in the mural endocardium of the left ventricle were present. At the area of application of the electrodes the epicardium showed varied patterns of inflammatory reaction, chiefly fibrinous hemorrhagic exudation in animals sacrificed early in the experiment and fibroblastic tissue proliferation in those allowed longer survival periods. Less severe and less extensive epicardial damage was apparently produced by the condenser discharge technique than by alternating current countershock. The regressive changes in the myocardium were likewise less severe, consisting in minimal muscle necrosis with occasional reactive phenomena and deposition of lime salts after longer periods of survival. In 6 of these 22 animals, neither epicardial nor myocardial lesions could be found by gross or microscopic observation.

Illustrations in figure 1 show some of the characteristic pathological changes observed in these hearts.

Conclusions

1. The pathologic effects on canine heart of fibrillation, countershock and manual compression have been studied. Survival experiments have permitted evaluation of the permanence of the damage produced.

2. Ventricular fibrillation produced diffuse vascular congestion, focal microscopic hemorrhage, edema and muscle fragmentation.

3. Massage of the normally beating heart produced minimal nonspecific damage. When the fibrillating heart was subjected to manual compression, the changes were somewhat more severe than those observed after fibrillation alone, and occasional focal myocardial necrosis resulted.

4. Alternating-current countershock produced both epicardial and myocardial damage at the site of application of the electrodes. The epicardial change was manifested initially as fibrinous hemorrhagic exudation and subepicardial fat necrosis, ultimately as fibrous tissue formation and pericardial adhesions. The myocardium revealed first necrosis, fragmentation and inflammatory reaction, and finally superficial fibrosis. In view of their localization, these changes would not be expected to alter cardiac function appreciably.

5. In the animals subjected to condenser-discharge countershock, the observed effect was of the same type as that produced by alternating-current defibrillation. Myocardial damage was not apparent in all these animals, however; nor was it as severe as that produced by alternating current. Further investigation would be required to determine the relationship between condenser-discharge countershock and the presence of mural thrombi in the left ventricle of 5 of these 22 animals.

6. The morphologic change resulting from alternating-current countershock was not apparently influenced by the type of electrode surface. Padding of the electrodes with saline-

soaked gauze did not appear to influence the degree of damage.

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SUMARIO ESPAÑOL

1. Los efectos patológicos de la fibrilación, contra choque y compresión manual en el corazón canino, han sido estudiados. Experimentos de supervivencia han permitido la evaluación de la permanencia del daño producido.

2. Fibrilación ventricular produjo congestión vascular difusa, hemorragia focal microscópica, edema y fragmentación muscular.

3. Masaje del corazón normal pulsante produjo cambios mínimos no específicos. Cuando el corazón fibrilante fué sujeto a compresión manual, los cambios fueron algo más severos que los observados luego de fibrilación solamente y ocasionalmente resultó en necrosis focal del miocardio.

4. Contrachoque con corriente alternante produjo daño al epicardio y miocardio en el sitio de la aplicación de los electrodos. El cambio en el epicardio se manifestó inicialmente como un exudado fibrinoso hemorrágico y necrosis de grasa subepicardial, finalmente como formación de tejido fibroso y adherencias del pericardio. El miocardio reveló primeramente necrosis, fragmentación y reacción inflamatoria y finalmente fibrosis superficial. En vista de su localización, estos cambios no se esperarían que alterasen la función cardíaca apreciablemente.

5. En los animales sujetos a contrachoque por descarga de condensador, el efecto observado fué del mismo tipo como el producido por la corriente alternante desfibriladora. Daño al miocardio no estuvo aparente en estos animales, sin embargo; ni tampoco fué tan severo como el producido por la corriente alternante. Más investigación sería requerida para determinar la relación entre contrachoque por descarga de condensador y la presencia de trombos murales en el ventrículo izquierdo en 5 de 22 de estos pacientes.

6. Los cambios morfológicos resultantes del contrachoque por corriente alternante no fueron aparentemente influenciados por el tipo de superficie de electrodo. Empaquetamiento de los electrodos con gasa mojada en solución salina aparentemente no influenció el grado de daño.

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CLINICAL PROGRESS

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Cardiovascular Problems in Pregnancy

By BURTON E. HAMILTON, M.D.

THOSE who give advice to pregnant cardiac patients must be prepared to discuss (1) maternal and infant death rate; (2) the risk of immediate invalidism; (3) whether maternal heart disease injures the infant. There are many other lesser but specific questions: What special care is needed in the hospital? When pregnancy is safely over, will the patient be able to care for her home and the child and for how long? How many pregnancies is it "safe" for her to undergo? How long should she wait between pregnancies? This summary does not pretend to answer all of these questions.

In giving advice it must be remembered that pregnancy is not a disease, but is a desirable process in varying degrees. Only the prospective parents know how desirable it is. Their purely personal desires are, among other considerations, the result of their religious and ethical beliefs and their wish for a particular child balanced against the risk of life and health. Presumably the twentieth child at age 40 would not be so welcome as the first at age 20. Within the framework of the law and medical ethics, the parents should make the decision for pregnancy and for therapeutic abortion. Whatever the physician's feelings and beliefs, they have no bearing on such decisions. In this summary, I am reporting my present opinion without intruding my religious or other personal bents.

Since we base our information on statistics, we should remember their weaknesses. It is obvious that, whatever the method of classification, individuals differ within each subclassification; in fact, each patient deserves special subclassification. We know that statistics lag. They do not keep up with progress in treatment. Accuracy requires a series of many cases which, if personally observed, are slowly accumulated. It is less obvious that statistics obtained from hospital records of cases followed by different individuals may not include deaths before delivery or in late puerperium because of transfer of cardiac patients from obstetrical to medical services. Patients may avoid or leave clinics where therapeutic abortions are not performed. Those that remain are a selected group. Those that go elsewhere may be worse than average risks. It is more accurate to base our information on risk of one year of pregnancy and puerperium compared with risk of living for one year not pregnant. Such statistics should be gathered from patients followed for a number of years before, after and during pregnancies.

Disturbances in respiration and circulation, in contour of the heart, fluid retention, and other circulatory phenomena with associated subjective symptoms that appear and change in varying degrees during normal pregnancy, are likely to confuse diagnosis and subclassification. The trained examiner soon learns from experience to make allowances for these disturbances.

RHEUMATIC HEART DISEASE

Many of the appropriate questions can be answered firmly for patients with rheumatic heart disease. Various clinics have reported *maternal mortality* for patients with rheumatic heart disease as less than 1 per cent to more than 3 per cent. This is fairly solid information. It can be compared with the risk of normal patients. Statistics indicate that the average maternal mortality rate for pregnancy and puerperium in cardiac patients of better subclassifications (including classes I and II o

the New York Heart Association classification) are only slightly higher than the mortality rate for one year of living not pregnant. For the minority who are severely handicapped (classes III and IV of the New York Heart Association classification) and have had signs of congestive heart failure under usual living conditions or during previous pregnancies, and for those with a complicating disease dangerous in itself, the risk of death during a year of pregnancy and puerperium is several times as great as for a year of living not pregnant. For those who have developed auricular fibrillation, the risk of pregnancy becomes still higher. Those that are classified in the majority (classes I and II) will be referred to as "favorable" cardiacs, others as "unfavorable."

The danger of heart failure and of death is, statistically, materially higher if the patient is 35 years of age or more. It is generally believed that *parity*, per se, is not a determining factor in maternal mortality of women with rheumatic heart disease.

Treatment markedly influences over-all maternal mortality among patients with rheumatic heart disease. Although the maternal mortality rate for the great majority, classified as "favorable" by any sound method, should be only slightly greater than the rate for one year of living, not pregnant, this is true *only* if the pregnant patient seeks and receives proper care. If not, no matter how skilled the strictly obstetrical care, the risk of death becomes nearly as great as if they were in the minority or "unfavorable" group. When cardiac clinics have been established in obstetric clinics, the maternal death rate has fallen impressively. This improvement has been in the "favorable" group. Although the treatment for congestive failure and other conditions has probably improved, the maternal mortality for the "unfavorable" patients has not improved in my experience. If the cardiac patient is severely handicapped, the unavoidable load of pregnancy leads to a high maternal death rate even with the best care.

One of the oldest cardiac clinics in an obstetrical hospital has reported a maternal death rate for "unfavorable" cases of 16 per cent for the first 15 years of the cardiac clinic. For the next 10 years, it was 18 per cent. The overall death rate for patients with rheumatic heart disease has continued to improve in this clinic. This is not due entirely to improved control and care of the "favorable" cardiac patients but relates to the decrease in proportion of "unfavorable" cases. The latter fact is noteworthy. Is the smaller proportion of unfavorable cases due to better care of cardiacs in general during the last 30 years following development of general cardiac clinics and more education of medical lay people? Is it because with education, fewer "unfavorable" cardiacs undertake pregnancy? Or is it because, as some believe, rheumatic fever is milder or better controlled?

It is believed by some observers that pregnancy, if survived without disaster, does not affect the course of rheumatic heart disease. This and the belief that rheumatic heart disease tends to progress in severity leads logically to *prognostication based on the number of years since the first attack of rheumatic fever.* The value of this hypothesis is limited because: (1) it is difficult to determine the time of onset; almost half of my private patients seen for the first time when adults, do not give a clear history of rheumatic fever; and (2) it has been convincingly shown that in children, the prognosis is much better during a 10-year period if the patient, immediately after the initial attack of rheumatic fever, has less than minimal evidence of rheumatic heart disease.

Age of the pregnant patient appears to me to be fully as useful as years elapsed since the first attack of rheumatic fever. In estimating prognosis, age is easily determined. Its effect is universal. However, both date of onset of first attack of rheumatic fever and age of the patient have only limited prognostic value. It must be remembered that wide variation in the course of rheumatic heart disease is common.

It is not possible to deduce clearly from the literature the *role of active rheumatic fever* in the course of pregnancy in patients with rheumatic heart disease. Though it has been suspected that pregnancy protects patients against activation of rheumatic fever, there is no clear evidence for this concept. Some of my

acquaintances who emphasize the role of rheumatic fever in determining the entire life course of adults with rheumatic heart disease believe that smouldering rheumatic fever is an important factor in prognosis in pregnancy. The general belief among experienced cardiologists of my acquaintance in this country is that pregnancy has little influence in activating rheumatic fever. Recent reports, however, of postmortem studies in small series, or in isolated cases, suggest that rheumatic fever in pregnancy, though rare, is the determining factor in maternal mortality of those with rheumatic heart disease. One report expressed belief that active rheumatic fever is a fatal complication in pregnancy. In my experience, recognizable rheumatic fever is rare in pregnancy, and only very slightly more common than in comparable nonpregnant patients, and the course is the same. It is a mistake to believe that rheumatic fever in pregnancy is uniformly fatal. The average age of my patients is just under 28 years. Recurrences have been many times more common in pregnancies among the young patients under 22 years of age than among the older ones. Possibly differences in average age of the patients or environmental conditions explain the discrepancy between my experience and opinions expressed in reports from other countries.

We have not enough data to be able to evaluate the desirability of *interruption of pregnancy because of rheumatic fever*. Whatever the role of active rheumatic fever in pregnancy of women with rheumatic heart disease, we need not feel that it alters the importance of other factors. Amount of heart damage, effort capacity, complicating disease, personality factors, age, and elapsed time since first attack of rheumatic fever, all are more or less proven to be significant. *The powerful beneficial effect of proper prenatal care on the immediate maternal and infant mortality rates in pregnancy of women with rheumatic heart disease is established for all time.* Since so many factors have been shown to influence prognosis, the natural temptation to overemphasize any one of them to make subclassification simple should be resisted. In the "favorable" groups, *infant mortality* is nearly the same as in the whole population. It is 30 per cent or more in the "unfavorable" group.

Does pregnancy tend to provoke or hasten invalidism and shorten life? Certainly it does in some cases. It is not clear that this is generally true if pregnancy is survived and has provoked no complication which leaves permanent damage. The incidence of heart failure occurring for the first time during pregnancy and puerperium appears clearly higher than for a year of living not pregnant. Statistics show that prognosis becomes poorer as soon as congestive heart failure has appeared, but prognosis may be little affected for many cases in which failure is induced by unusual stress and is promptly relieved after stress is avoided. Much has been made of reports that women with rheumatic heart disease who have *borne children and have survived pregnancy* live as long or slightly longer than women with rheumatic heart disease who have not been pregnant. This is interesting, indeed, but does not permit the conclusion that pregnancy, per se, does not shorten life expectancy, other factors being equal. They are not equal. Obviously those that marry are a selected group. The unhandicapped are more likely to marry than those who are invalided, some of whom are confined to institutions. This is indirectly but convincingly supported by vital statistics on married versus single women in five-year periods, in the general population. During the years when the majority of marriages occur, the difference is great. Mortality rates are much higher among unmarried women. Furthermore, it seems likely that the average married woman has an easier life, particularly after age 35 when invalidism and death among rheumatic heart disease patients become frequent. Often the cardiac patient receives considerable assistance from her husband and grown children. Most of the spinsters are self-supporting and life becomes no easier.

Statistics which show that the more pregnancies a cardiac patient has had, the older she is at death, are seldom interpreted to indicate that a cardiac who wants to live a long time should have all the children she can, though this has indeed been implied. Proof is

still lacking that pregnancy, per se, does not shorten life expectancy even when deaths during pregnancy and puerperium are excluded.

The question, *"Shall I live long enough to see my children grow up and may I expect to be able to care for them?"* can be answered fairly firmly. However highly we value available statistical reports that those that have married and had pregnancies live at least as long as those that have not had pregnancies, we must not, in advising patients, let this obscure the fact that expectation of sustained capacity for ordinary effort and for life are materially shortened by *rheumatic heart disease*. Occasional reports familiar to internists, but not to the laity, continue to confirm this. Nor should we withhold the fact from the laity that early invalidism and midlife death are not inevitable. Occasional reports emphasize the fact that some women with rheumatic heart disease function well and live to good age. Because of expected early invalidism and premature death, some physicians urge that cardiac patients be advised to *have their pregnancies only in early life*. Studies by psychologists show that the average female with rheumatic heart disease is *psychosexually retarded* and less fitted physically and emotionally for all the demands of married life. There are numerous exceptions, of course. But the average patient is more dependent than comparable normal persons. She should be.

Since the majority of young women with rheumatic heart disease marry and the great majority of those married undertake pregnancy, and since success depends in part on planned living and cooperation from the patient's family, *timely education* for all concerned is needed. Treatment of pregnancy for cardiacs logically begins in the period before marriage.

Surgery for Rheumatic Valvulitis during Pregnancy

There are a few reports of successful surgical treatment of the mitral valve during pregnancy. No one could be satisfied with this as a plan for usual procedure. The need for surgery during pregnancy should be avoidable, except in rare circumstances, if cardiacs receive timely education.

Nonpregnant patients with a high degree of mitral stenosis, normal rhythm and nearly normal heart size, but with attacks of acute pulmonary edema and severe dyspnea and rapid heart rate, sometimes with chest pain and hemoptysis, are believed to benefit greatly by prompt surgical treatment. Pregnancy is especially likely to provoke the symptoms just described. Typically, the seizures recur until the pregnancy is over and then disappear, at least temporarily. Some patients die undelivered. Most of the cases that I know about have had interruption of the pregnancy because of increasingly violent symptoms recurring with increasing frequency, with cessation of the attacks following termination of pregnancy. A few, who have had little restriction of activity until the seizures appeared, whose seizures began late in pregnancy and who were then treated with great care, have attained successful term delivery. It is a dramatically dangerous syndrome, familiar to most internists but far from common. Clearly defined cases occur in hardly more than 1 in 100 pregnancies of women with rheumatic heart disease. Some consider that surgical treatment of the valve disease is indicated promptly when this syndrome appears in the early months of pregnancy if the condition of the patient can be rendered satisfactory for the operation. The alternative is to interrupt the pregnancy. From my experience, it is hard to justify withholding both interruption and immediate surgical treatment of the valve when these symptoms appear early and recur in spite of medical treatment. Since interruption may be expected to abolish the symptoms for a long time if the patient is kept under control, and since surgical treatment of the valve, without the complicating load of pregnancy and after ample time for convalescence, should make later pregnancies safer, interruption first and surgery later seems the safer method. There is uncertainty at present concerning the immediate response to surgery, and uncertainty in regard to the time required for optimum improvement after operation.

In the far more numerous patients with rheumatic heart disease who do not belong in the group discussed above, but who are seen in

early pregnancy in chronic congestive failure or who have early failure that responds slowly to standard treatment, the choice between immediate surgery, interruption with surgical treatment later, or allowing pregnancy to continue, relying on medical care alone, is indeed difficult. We can only compare immediate surgical mortality with mortality rates of patients in similar subclassifications. At present, it appears to me that the choice must be made rather blindly. We need to know much more about the course during the months immediately following cardiac surgery of young women operated on when not pregnant. Certainly not all of them show immediate improvement. Some improve after a considerable delay. It is reasonable to believe that recovery from surgical treatment would be affected by pregnancy. The fact that some cases have been operated on during pregnancy successfully does not alter the fact that, in general, recovery from a stress is retarded by addition of other stresses. It is good sense, at this time, to keep an open mind, and to recognize the need of educating patients to have their cardiac status assessed before undertaking pregnancy.

Congenital Cardiovascular Defects

Statistics are necessarily less satisfactory for these than for the common cardiac diseases.

Patent Ductus Arteriosus

The maternal mortality rate is probably no better than for patients with rheumatic heart disease, namely, between 3 and 4 per cent. The same may be said less confidently for infant mortality. Those with large hearts, pulmonary blood vessel congestion, low effort capacity, high systolic and wide pulse pressure, probably tolerate pregnancy less well than those in whom these changes are not as extreme. There is evidence that the blood pressure of these patients rises materially some days before and remains elevated until term delivery and then drops suddenly after delivery, though this does not occur in every instance. There is no such drop in blood pressure after delivery in normal women after uncomplicated delivery. A few patients with patent ductus arteriosus have been reported in whom death followed promptly after delivery. There is some evidence that a right-to-left shunt developed at the time of the drop in systemic blood pressure and was the cause of sudden death. Postmortem examinations in some of these cases have shown a very large patent ductus. As might be anticipated, a moderate number of patients who have been successfully treated surgically for patent ductus have done well in pregnancy.

Should patients already pregnant have surgical treatment of this anomaly at once? Perhaps. It has been done successfully. Recovery from this operation should be easier than from surgical treatment of rheumatic mitral stenosis. Improvement in the circulation should be immediate. Healing of the vital vascular organs should be prompt and should not make heavy demands on the body. There is not apparent, therefore, any great advantage to be gained by interruption of the pregnancy first and surgical treatment later. Obviously this situation need not occur if patients have adequate premarital physical examinations and plan their pregnancies.

Septal Defects and Pulmonary Stenosis

Pregnancies among cardiacs with *ventricular septal defects* have not been reported as frequently as among those with patent ductus. From my experience and from available data, the maternal and infant mortality are approximately the same for both conditions. It is generally believed that patients with *auricular septal defects, and those with Lutembacher's Syndrome* tolerate pregnancy well. A few experiences make me hesitate to accept this dictum when there is marked cardiac enlargement. The same may be said for patients with *pulmonary valve stenosis.* For some reason, there are less data for *pulmonary stenosis* in pregnancy than for the two defects previously discussed. In my experience, sexual development has been more retarded and fertility less lasting among those with pulmonary stenosis. So few instances of pregnancy in women with *Tetralogy of Fallot* have been reported that such rare occurrences must be treated without the aid of adequate experience. Sudden, severe symptoms directly after

emptying the uterus attributed to aggravation of the right-to-left shunt have been reported. Little is known about the course of pregnancy in patients who have had surgical treatment for Tetralogy of Fallot.

Relation of Maternal Anomalies to Fetal Congenital Cardiac Anomalies

Deaths have been reported of patients with patent ductus, Roger's disease or pulmonary stenosis, with the same cardiovascular defect found in the fetus at postmortem examination. Some of these women had been previously delivered of healthy infants. Women with developmental cardiovascular defects thus face the chance, however slight, of a specific defect in the infant that the mother with acquired heart disease does not face. There are also reported instances of similar cardiovascular defects in father and child.

Coarctation of Aorta

Pregnancy for patients with coarctation of the aorta has received considerable attention. Some observers have reported a high maternal death rate. But where the maternal mortality percentage is based on the number of pregnancies rather than on the number of individual patients, the mortality rate is not alarmingly increased. It has been noted that women with coarctation of the aorta stand approximately an even chance of having a lower blood pressure during pregnancy than at other times, and are likely to say that they are more comfortable when pregnant. There is an almost equally good chance that blood pressure will rise alarmingly in the latter part of pregnancy, at times accompanied by lowered effort capacity, spells of breathlessness, and encephalopathy. Cases have been reported of lower blood pressure in one pregnancy, higher pressure in a later pregnancy, and vice-versa.

Dissection of the aorta. Among the few reported maternal fatalities, dissection of the aorta is prominently mentioned as the immediate cause. A few have survived the dissection and lived for months. It has been suggested that patients with coarctation of the aorta should be delivered by caesarian section before labor begins to avoid the apparent strain of labor. This rule, if adopted, might also apply for pregnancies in women who have had surgical treatment of coarctation of the aorta.

The group with dissection of the aorta without accompanying coarctation is of interest. Nearly half of the reported women of child-bearing age who have died of dissection of the aorta were pregnant or in the puerperium. Only a few had coarctation of the aorta. Hypertension is often present, but a large number had neither coarctation nor hypertension and showed characteristic medial necrosis of the aorta. Atherosclerosis was not the underlying pathology. There is, then, apparently some association between disease of the media and pregnancy. The mobilization of cholesterol in pregnancy has been suggested as a possible factor but without supporting evidence.

It would seem that a thorough study of the effect of pregnancy on the aorta is desirable. This would have a direct bearing on indications for surgical treatment of coarctation of the aorta during pregnancy. Successful surgical treatment of coarctation in the early months of pregnancy has been performed. However, one case, not yet formally reported, which was operated upon in the first few weeks of pregnancy with good immediate results, ended in rupture of the aorta in the eighth month. Though the author believes that the last trimester of pregnancy, or delivery, are the periods most dangerous for women with coarctation of the aorta, rupture or dissection of the aorta due to disease of the media alone may occur at any time in pregnancy. There have been reported a small number of patients who were treated surgically for coarctation of the aorta and who had subsequent successful pregnancies.

Comment

Many *rare congenital cardiovascular defects* and pregnancy have, of course, been reported and discussed, but data are insufficient to warrant conclusions. How much pregnancies affect the *life course of women with congenital cardiovascular defects* is less clearly known than the effect of pregnancy on acquired heart

diseases. We must wait many years before really satisfying statistics on pregnancy for surgically treated cases of the various cardiovascular defects can be gathered. Such data should be collected, however, particularly by clinics and individuals performing such surgery on large numbers of patients.

Women with congenital cardiovascular defects should reasonably have the same prenatal observation and general care as female cardiac patients in general. I make it a rule to be present at delivery and for a while thereafter when my patients with an arteriovenous communication are delivered. If distressing symptoms appear, binding of extremities, abdomen and limbs or tourniquets on the limbs to reduce venous flow, or dropping the legs, or all three and other appropriate emergency measures, may be in order. At any rate, those responsible for the cardiovascular condition of the patient should remember that there is a time of special danger for the mother directly after delivery.

Bacterial Endocarditis (Acute and Subacute)

In my experience before the era of modern treatment, bacterial endocarditis occurred in slightly less than 1 per cent of pregnancies with rheumatic heart disease or congenital cardiovascular defects. Since then, the incidence has declined. Treatment during pregnancy is fairly satisfactory, especially if the disease is discovered early and before there is general depletion and widespread pathology. I believe that treatment during pregnancy is somewhat less successful than under usual conditions. In my limited number of cases, pregnancy apparently hastened the progress of the disease. In spite of early diagnosis and modern treatment, two patients died with multiple, widespread hemorrhages; both fetuses died in utero from intracranial hemorrhage. In contrast, there had been almost no difficulty in controlling symptoms promptly in comparable young, nonpregnant women and young men, in whom the diagnosis was made equally early and before widespread symptoms appeared. It is worthwhile to continue study of this subject until statistics are adequate. If it were clear that pregnancy interferes with treatment materially, prompt therapeutic abortion should improve the chance for the patient's survival and future successful pregnancies.

Subacute bacterial endocarditis is somewhat more likely to be discovered in the few months following pregnancy than during pregnancy. At delivery and in early puerperium some form of prophylactic therapy against bacterial endocarditis is generally advocated for patients with rheumatic and congenital cardiovascular disease. How long this treatment should be continued has not yet been sufficiently studied.

After cure of subacute bacterial endocarditis pregnancies are generally satisfactory. There appears to be little reason to fear pregnancy in recovered cases because of this danger alone, though recurrences have been reported. Prophylactic treatment throughout pregnancy and early puerperium has been advocated.

Essential Hypertension

The course of pregnancy for patients with essential hypertension is not as well documented as pregnancy for patients with rheumatic heart disease. This is probably due in part to the difficulty in defining and subclassifying essential hypertension, of differentiating it from pre-eclampsia–eclampsia, and in identifying the patient who has both. Since obstetricians are constantly alert for hypertension, they have developed special skill in the recognition of pure or complicated pre-eclampsia–eclampsia, and knowledge of its course. Nevertheless, it is the internist or cardiologist who is commonly asked by the patient with chronic hypertension for information concerning the effect of pregnancy.

A fair number of statistical reports are available on maternal and infant mortality. The *maternal death rate* appears to be somewhat lower than for patients with rheumatic heart disease. As in rheumatic heart disease, the maternal death rate is pleasingly low in the first and second groups, as subclassified on a scale of four, but high in the much smaller groups with severe essential hypertension classified as group III or IV.

There is general agreement that a large

percentage, often placed at 30 per cent or more, develop *pre-eclampsia*. However, it is often difficult to be confident that symptoms developing late in pregnancy are due to pre-eclampsia and not to the progress of essential hypertension. But careful studies continue to reduce this difficulty. The criteria for differential diagnosis cannot feasibly be discussed here, though they are of interest to internists. For example, studies in patients with (1) essential hypertension, (2) pre-eclampsia, and (3) both together, indicate interestingly that cardiac output is not increased in 1, slightly increased in 2, and materially increased in 3. Circulating blood volume apparently is somewhat below average in women with toxemias when compared with normal women at the same stage of pregnancy.

There is general agreement that there is a heavy infant mortality, particularly among patients who are in the severe subclassifications. There is general agreement that timely interference with the pregnancy is a particularly important factor in infant survival.

Some believe that essential hypertension does not materially increase the risk to mother and child. Unquestionably, however, adequate experience shows that pregnancy may cause alarming symptoms in some patients with essential hypertension, and that where the symptoms are alarming, there is a heavy infant mortality. It also can be accepted as proven that there is high maternal mortality among those with essential hypertension who have enlarged hearts, and who have had symptoms of congestive heart failure or seizures of paroxysmal dyspnea, or have evidence of severe nephritis. Statistics indicate that the *age of the patient* is a potent factor in mortality rates.

Impressive statistics indicate that the condition of the eyegrounds is the single most important point in prognosis for infant mortality, and that regardless of the status of the mother on other findings, if the eyegrounds are in class I or class II, the prognosis for the infant is good. If in class III or IV, the prognosis for the infant is bad.

It is also generally believed that skillful *prenatal control*, especially by obstetricians, favorably affects infant and maternal mortality of patients with essential hypertension. Maternal and infant mortality rates in essential hypertension have improved during recent years. It has been reported that where prenatal *weight control* and *sodium restriction* have been enforced, there is marked lowering of the maternal and fetal mortality rates whereas in localities where this treatment has not been carried out, no such improvement has occurred. Some impressive statistics gathered many years ago showed that the same may be said for care of *oral sepsis*.

Hormonal treatment during pregnancy, as a preventive measure, has been followed by improved statistics in some clinics.

It is certain that the factors which are responsible for the development of severe symptoms of essential hypertension in pregnancy are not yet as sharply defined as the factors related to congestive heart failure in rheumatic heart disease. It has been stressed, for example, that pre-eclampsia and eclampsia, more or less intermingled with essential hypertension, are much more common in unwanted pregnancies, for example, in illegitimacy, and in the third pregnancy. In general, the emotional and personality factors in the course of essential hypertension have attracted more attention in relation to pregnancy than in relation to rheumatic heart disease.

How does pregnancy affect the life course of patients with essential hypertension? From the above considerations, the conclusion must be that, other factors being equal, pregnancy shortens life expectancy statistically to some extent. In one large series of women with essential hypertension studied by me but not yet reported, the percentage in the severe subgroups was higher in women who had borne children than in those of the same age who were childless.

Recent reports suggesting that essential hypertension does not shorten life expectancy materially except in approximately 5 per cent of subjects should not lessen the force of well-known reports nearly 20 years ago of hundreds of women who had hypertension-albuminuria during pregnancy and survived, but who, after

being followed for more than seven years, were found to have a mortality rate five times higher than that for women of the same age in the community at large. Eighty per cent of the deaths were cardiovascular. One cannot at present distinguish clearly each good and bad risk before pregnancy.

Medical treatment of essential hypertension in pregnancy from the point of view of the internist is the treatment of essential hypertension in general. Patients deserve careful and continued observation, protection against fatigue, needless weight gain, malnutrition and complicating disease, just as do those with rheumatic heart disease, and, so far as is feasible, protection from all stresses known to affect hypertension. Many consider pregnancy a formidable stress for patients with essential hypertension.

Does pre-eclampsia–eclampsia cause heart disease, and if so is it permanent? I believe that the normal heart may be affected but apparently less so than many other organs. The pathology is not specific. Cardiac output is only slightly increased. Cardiac deaths in patients with uncomplicated pre-eclampsia and eclampsia must be rare if, indeed, they occur. Nevertheless the heart not infrequently appears to be enlarged in those believed to have uncomplicated, severe pre-eclampsia or eclampsia. There are gallop sounds; the rate may be rapid with pulsus alternans; there usually is rapid breathing, often rales and generalized edema. Sometimes acute edema of the lungs occurs. Circulating blood volume is, however, usually surprisingly low, lower on the average than for normal patients at the same stage of pregnancy; the usual evidences of congestive heart failure associated with high circulating blood volume are absent. When, however, pre-eclampsia complicates rheumatic heart disease, signs of congestive heart failure usually appear quickly. Electrocardiographic studies have failed to show convincing evidence of severe myocardial change in uncomplicated cases in my experience, although a few case reports have described such evidence.

Careful follow-up of somewhat small groups, divided so far as possible into (1) mild pre-eclampsia, (2) severe pre-eclampsia, and (3) eclampsia, showed that patients in the first group exhibited a high incidence of hypertension and hypertensive heart disease; many individuals in this group were believed to have essential hypertension and were wrongly classified as mild, but pure, pre-eclampsia. In patients in the second group, where evidences of pre-eclampsia were more definite and fewer patients with essential hypertension were wrongly included, there was much less evidence of hypertension and heart disease. Those in the third group, probably correctly classified as pure, uncomplicated eclampsia, almost without exception had normal hearts and blood pressure, a dramatic finding in view of the severe symptoms during the height of the eclampsia. It indicates that pure pre-eclampsia-eclampsia seldom if ever causes permanent heart disease.

Physiology of Circulation during Pregnancy

The physiology of the circulation during pregnancy will be briefly summarized. Widely known studies reported more than 10 years ago revealed increased circulating blood volume and cardiac output, moderate hemodilution, increased heart rate, hurried circulation, a slight fall in blood pressure and increased pulse pressure, returning toward normal in the final phase of pregnancy. The basal oxygen consumption was found to be increased slightly. There was a slight increase in the vital capacity and a greater increase in minute-volume of respiration. Studies of many other allied phenomena were also available. A fairly distinct outline of the circulatory changes and of the total load on the circulation became apparent. Of particular importance was the usually slow development of increased work of the heart until during the early part of the last trimester when it abruptly increased, with subsequent levelling off until the last three or four weeks of pregnancy, when the previous increase in cardiac work and output gradually lessened to a material degree until term. This curve resembled a curve based, in a long series of cases, on the time in pregnancy when

symptoms of heart failure first appeared. The lightening of the load in the four weeks before term had long been noted but not generally appreciated. Demonstration and measurement by indirect tests attracted attention and led to modification of the obstetric care of patients with cardiovascular complications. In particular, there were fewer interruptions for cardiovascular reasons during the last trimester and, therefore, fewer hysterotomies. Since then, there have been numerous similar studies by improved technics that have essentially confirmed the conclusions previously indicated. The changes vary in extent and in timing, but there is always an increase in the load which partly disappears near term in normal pregnancy. Later studies have extended into the puerperium and indicate a gradual return toward normal over several weeks.

The abrupt changes that accompany emptying the uterus and detachment of the placenta with sudden removal of the circulatory system of the infant must affect the mother profoundly. The average patient who is in heart failure when delivered, instead of experiencing immediate relief after delivery, is worse. This obtains even when delivery is precipitate and apparently effortless. Some patients with arteriovenous communication suddenly develop or increase a venous-arterial shunt.

Distressing symptoms after delivery may be due to an abrupt fall, reported to average 250 cc., in vital capacity consequent to suddenly decreased intra-abdominal pressure. Many other disturbances are probably also strongly implicated; these include increase in congestion of pulmonary vascular bed at term and delivery. Further investigations concerning the extent and course of this increased congestion of pulmonary blood vessels are highly desirable. Does it appear constantly? Does it appear before labor begins? Release of pressure on the pelvic and leg veins and contraction of the emptied uterus seemingly flood the maternal veins and lead promptly to pulmonary congestion. After detachment of the placenta, amniotic fluid may invade the veins in significant quantity and increase pulmonary congestion. Obstruction of small pulmonary vessels by the particulate matter in amniotic fluid, though only rarely believed to be a significant danger, may be important in hard-pressed cardiac patients with chronically engorged pulmonary blood vessels. Some believe that the distress of cardiac patients after delivery is provoked by use of drugs that have a pressor effect. But distress appears in hard-pressed cardiacs even when delivery is precipitate and appears effortless and when no pressor drugs have been administered. Catheterization during labor and delivery is wistfully regarded as a likely method for illuminating these matters. So far, very few reports have appeared, to my knowledge. Technical and other difficulties and fear of disaster have discouraged nearly all with whom I have discussed this method of study. Many simple studies by left auricular catheterization some time before delivery and some time after delivery have been reported. They throw little light on the problem of what happens during delivery and immediately or soon thereafter.

If we knew the time and extent of pulmonary congestion before, during and after delivery, and the mechanism thereof, it is possible that we might control the process sufficiently to aid the occasional woman who goes into labor or who must be delivered while in heart failure. Certainly, we can consider methods for restoring intra-abdominal pressure to reduce critical respiratory embarrassment after delivery, such as our every day procedures in treating emphysema. Flooding of maternal veins after release of pelvic pressure can be controlled, to some extent, by tourniquets and by dropping the legs. These maneuvers have been tried, but surely are not in general use and need to be supported by suitable studies. Even the chance of amniotic embolism might be partly controlled if the need for this were clear. If indirect support for these procedures is not to be expected, it nevertheless would be well to assess their possible benefit.

Disturbed fluid balance in pregnancy, and also in phases of the menstrual cycle and in menopause, is receiving somewhat belated attention by internists, particularly in women

with mitral stenosis. In some women, the disturbances are profound. The great interest in the physiology of fluid retention and edema in heart disease should clearly include this problem. In obstetric clinics, interest in fluid retention is intense. Progress through continued study of hormone behavior seems likely. This surely concerns cardiologists. The mechanism of blood dilution, increased circulating blood volume, and hurried circulation in pregnancy, needs study. These phenomena, though normal in pregnancy, may not be desirable in cardiac patients and might be influenced. More active study of the physiology of the circulation in pregnancy, delivery and puerperium also may lead to improved treatment of every day congestive heart failure, particularly in women.

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ABSTRACTS

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BACTERIAL ENDOCARDITIS

Hamburger, M., and Knowles, H. C.: Streptobacillus Moniliformis Infection Complicated by Acute Bacterial Endocarditis. Arch. Int. Med. **92:** 216 (Aug.), 1953.

A 54 year old physician, known to have previously had a normal heart, was bitten by a laboratory rat. He rapidly became ill, with the development of a loud mitral systolic murmur. *Streptobacillus moniliformis* was grown from his blood. He was treated with penicillin and recovered.

It might prove the course of wisdom to administer penicillin as a prophylactic measure for two or three days following a rat bite in laboratory personnel.

BERNSTEIN

Parsons, W. B., Cooper, T., and Scheifley, C. H.: Occult Subacute Bacterial Endocarditis Manifested by Hematologic Abnormalities, Including Pancytopenia. Ann. Int. Med. **39:** 318 (Aug.), 1953.

Data have been presented on three cases which illustrate the difficulty in diagnosis which may arise when hematologic abnormalities overshadow the "classic" manifestations of subacute bacterial endocarditis. All three cases showed anemia, which we have found to be present in 75 per cent of cases of the disease. One case had pancytopenia which has not been present in any case previously reported in detail. It is emphasized that the association of a cardiac murmur and an unexplained anemia or of an unexplained fever and anemia should suggest the possibility of bacterial endocarditis.

WENDKOS

BLOOD COAGULATION

Wolff, J. M., Barker, N. W., Gifford, R. W., and Mann, F. D.: Experience with A New Intravenous Coumarin Anticoagulant (Warfarin, Sodium Derivative). Proc. Staff Meet., Mayo Clin. **28:** 489 (Sept.), 1953.

Warfarin (sodium derivative) was safely administered intravenously to 29 patients and was effective in producing hypoprothrombinemia in all of them. The hypoprothrombinemia reached the therapeutic range within 24 hours after administration of warfarin (sodium derivative) in 26 of the 29 patients. In one hypersensitive patient with an indwelling catheter, gross hematuria followed the intravenous injection of Warfarin (sodium derivative). No other bleeding or untoward reactions were encountered. Vitamin K was effective in rapidly correcting hypoprothrombinemia caused by Warfarin (sodium derivative) in all three patients on whom it was used.

SIMON

Fullerton, H. W., Danie, W. J. A., and Anastasopoulos, G.: Relationship of Alimentary Lipaemia to Blood Coagulability. Brit. M. J. **2:** 250 (Aug. 1), 1953.

Using viper venom as source of thromboplastin the authors purport to have demonstrated a reduction in prothrombin time after a fatty meal. The degree of reduction paralleled the degree of lipemia. When other sources of thromboplastin, such as acetone (dried extracts of rabbit brain) were employed, this phenomenon was not observed because, the authors believe, these other thromboplastins contain much lipoid material which provides an essential factor in excess and masks the effects of lipemia.

Coagulation time in silicone-coated tubes was also determined. After an ordinary ward breakfast no change in this test was usually seen. After a high fat meal, as in the case of the prothrombin time, coagulation time was reduced significantly in 13 cases

in which gross lipemia developed. In two cases without gross lipemia no change occurred.

The authors suggest a relationship of their observations to the pathogenesis of arteriosclerosis.

McKusick

Utz, J. P., Mann, F. D., and Barker, N. W.: Clearing of Lipemic Plasma by Heparin Duration of Effect and Other Studies. Proc. Staff Meet., Mayo Clin. **28**: 531 (Sept.), 1953.

Studies are reported of the clearing effect of intravenous heparin on lipemic plasma induced after a fatty meal in a total of 69 atherosclerotic and control patients. In 11 of 12 patients who received a dose of 3 mg. of heparin, the clearing of the plasma did not persist for one hour. When the dose of heparin was increased to 20 mg. the clearing effect failed to persist for two hours in all 10 patients who were tested. When heparin and the fatty meal were given simultaneously in 11 patients, no detectable difference was noted in the average degree of lipemia three hours later. The intravenous injection of 100 mg. of heparin per day for three days changed the response toward normal in four atherosclerotic patients. A similar effect was not noted in three atherosclerotic patients who did not receive heparin between tests.

Simon

Loewe, L., Richmond, G., Brown, R., Lasser, R. P.' Cohen, C., and Cox, H.: The Effect of Repository Heparin upon Lipoprotein Patterns in Human Beings. Angiology **4**: 295 (Aug.), 1953.

In 57 patients, including individuals with and without clinical evidence of atherosclerosis, the relation between repository heparin and serum lipoprotein patterns was studied. Blood samples were obtained in the fasting state, in the fasting state four hours after heparin injection, and while on a regular diet at 12, 24 and 48 hour intervals after heparin administration. Serum lipoprotein analyses were performed by ultracentrifugation according to the method of Gofman. It was found that the most pronounced effect was upon the lipoproteins in the S_f 35–100 range, wherein their concentration four hours after the injection of the repository heparin was reduced about 80 per cent. No significantly different responses occurred with heparin doses ranging from 200 to 400 mg. On the average the effect lasted 24 hours.

Wessler

CONGENITAL ANOMALIES

Stein, F.: Delta Shaped Origin of a Coronary Artery from the Aorta and Pulmonary Artery and its Embryologic Explanation. Arch. Kreislaufforsch. **19**: 356 (Aug.), 1953.

The author describes an unusual anomaly found at autopsies of two cases (11 weeks and 23 years old) with congenital heart disease. The aorta originated from both ventricles via a high ventricular septal defect, and the pulmonary artery was hypoplastic and completely atresic at its ostium. Its distal portion was supplied by a large branch of the left coronary artery in the first, and of the right coronary artery in the second case. Thus, in these two instances, conditions were present comparable to those created artificially by the Blalock operation, in which a systemic artery is implanted into the pulmonary circulation.

The pathogenesis of this rare anomaly can be explained on the assumption of a faulty rotation of the aortico-pulmonic septum. Instead of separating the endothelial buds of the common truncus, the anlage of the coronary ostia from the pulmonary circulation, the septum meets and splits one of the buds into two portions with the result of a double origin of the afflicted coronary vessel—one ostium being located in the aorta and the other in the pulmonary artery.

Pick

Espino Vela, J., Muchinik, J., Comas Leal, M., and Saaibi, E.: Distal Aorto-Pulmonic Fistula. Arch. Inst. cardiol. Mexico, **23**: 461 (Aug. 31), 1953.

The authors describe four cases of aorto-pulmonary fistula at the site of the ductus. Three of the cases had evidence of right ventricular strain. In two cases, the diastolic component of the murmur was much louder than the systolic. The electrocardiogram of three cases had a pattern of right axis deviation and right ventricular "strain." The pulmonary artery was extremely dilated. Two of the cases had cyanosis, a third presented a late cyanosis. Two of the patients died in failure, one died of bacterial endocarditis and pulmonary tuberculosis, while the fourth died in a state of vascular collapse. Autopsy revealed aortopulmonic fistula, extreme dilatation of the pulmonary vessels and right heart, and, in one case, hypoplasia of the aorta and left heart.

The difficulty of the diagnosis is due to the atypical picture. Surgery requires development of a special technic.

Luisada

Levinson, D. C., Griffith, G. C., Cosby, R. S., Zinn, W. J., Jacobson, G., Dimitroff, S. P., and Oblath, R. W.: Transposed Pulmonary Veins. A Correlation of Clinical and Cardiac Catheterization Data. Am. J. Med. **15**: 143 (Aug.), 1953.

The authors describe the clinical and cardiac catheterization data in 10 patients with transposed pulmonary veins. The diagnosis in these cases was made at cardiac catheterization by roentgen visualization of the catheter in the anomalous vein, by a characteristic pulmonary vein pressure curve and finally by 90 to 95 per cent oxygen saturation in the blood sample from the anomalous vein. Surgical exploration to correct this anomaly should be reserved for patients with complete transposition in whom limitation of physical activity is progressive. The authors report one case successfully treated by an

anastomosis of the main trunk of the left pulmonary veins to the left auricular appendage. A second patient in whom a similar operation was attempted expired suddenly several hours after the surgery.

Patients with partial transposition of the pulmonary veins as the sole anomaly have few, if any, symptoms, and usually have normal growth and development. Patients with complete transposition were small of stature and considerably underweight. The heart, normal in size in the patients with partial transposition, was moderately enlarged in patients with complete transposition. Pulmonary systolic murmurs were present in all patients. Roentgenograms of the chest showed increased prominence of the pulmonary artery segment. Fluoroscopy revealed increased pulsations of the pulmonary arteries. Angiocardiography in five of these patients was of no aid in detecting the anomalous pulmonary vein or the presence of an atrial septal defect. The electrocardiogram showed right axis deviation with the pattern of incomplete right bundle branch block in the two cases of partial transposition. With complete transposition there was right axis deviation with a very tall R wave in V_1, the pattern of right ventricular hypertrophy.

HARRIS

Alden, J. F., Haddy, F. J., Sprafka, J. L. and Baronofsky, I. D.: Study of the Cardiodynamics of Experimental Pulmonary Stenosis. Ann. Surg. **138:** 209 (Aug.), 1953.

This study was carried out on dogs because of the difficulty of encountering a large series of humans with severe pulmonary stenosis, and also because some of the experimental procedures, such as left heart catheterization, are too hazardous to be done on humans. Whereas in previous studies the stenosis was developed in the pulmonary artery, in the present study stenosis was made in the infundibulum. This was done by passing two mattress sutures across the pulmonary conus and tying them over small pearl buttons. In this way the pulmonary conus was plicated and the infundibulum made stenotic. Catheterization studies were done and pressures were recorded in the pulmonary artery, right ventricle, right atrium, pulmonary vein, left ventricle and aorta simultaneously with the intrathoracic pressures. Oxygen content of arterial and venous blood was measured and the cardiac output was determined by the direct Fick method. Right ventricular pressures indicate that the degree of stenosis in these animals is comparable to moderate to severe pulmonary stenosis in the human. The course of the adult animals indicates that a severe stenosis may produce chronic right heart failure in as short a time as nine months. It would also appear that a reduction in area of the right ventricular outflow orifice of 75 to 85 per cent is needed to produce failure in a relatively short period of time. Clinically, the urgency for surgery in cases of pulmonary stenosis is customarily based on right ventricular pressure. This may not be well founded physiologically, since pressure depended on too many variables. The same holds true for cardiac output. The authors believe that an accurate estimate of the area of the right ventricular outflow orifice would be the best criterion upon which to base the need for surgery.

DENNISON

Swan, R. D., and Cooley, R. N.: Congenital Pulmonary Arteriovenous Aneurysm. Am. J. Roentgenol. **70:** 183 (Aug.), 1953.

The authors summarize the literature and present nine cases proven by operation, angiocardiography or laminagraphy. Fundamentally the lesions are hemangiomatous in nature, the majority being cavernous hemangiomata with large vascular channels permitting varying degrees of arteriovenous shunt. Physiologic disturbances, when present, are secondary to the shunting of unoxygenated blood back to the left side of the heart with resultant anoxemia and a polycythemic response of varying intensity.

Dyspnea, epistaxis, cerebral disturbances (secondary to polycythemic arterial thrombosis), hemoptysis and chest pain were not uncommonly noted; continuous or systolic murmurs, cyanosis, clubbing and cutaneous hemangiomata were frequently found. Polycythemia was the rule except when epistaxis or hemoptyses resulted in lowered red blood cell counts.

SCHWEDEL

Lurie, P. R.: Postural Effects in Tetralogy of Fallot. Am. J. Med. **15:** 297 (Sept.), 1953.

Alterations in the volume of venous return with consequent change in the oxygen saturation of mixed venous blood are responsible for the postural effects upon cyanosis and dyspnea in the tetralogy of Fallot. These postural effects include the beneficial effects of the squatting and knee-chest position and the more detrimental effect of the standing position. Speculations are adduced to explain the peculiarly marked effect of altered venous return in malformations when there are venoarterial shunts, reduced pulmonary blood flow coexisting with high systemic flow and absence of a tendency to go into congestive heart failure. Diagnostically, these postural effects are important when they can be demonstrated in the form of simple clinical tests. A patient demonstrating them will respond well to systemic-pulmonary anastomosis. Therapeutically they are of real importance in carrying a patient through the period of waiting for definitive surgery.

HARRIS

Souliè, P., Joly, F., Carlotti, J., Pitton, A., and Thaillez, B.: Moderate Pulmonary Valvular Stenosis. Arch. mal. coeur **8:** 695 (Aug.), 1953.

Among 32 cases with pulmonary valvular stenosis

10 cases were found in whom clinical and hemodynamic data indicated a moderate degree of the lesion. The essential common features of this group were: good functional capacity, a small heart shadow with a distinctly pulsating prominence at the left border which corresponded to an ovoid dilatation of the main pulmonary artery as revealed in angiocardiograms and only slight electrocardiographic alterations which suggested right heart strain. Although there was a definite pressure gradient between the right ventricle and the pulmonary artery, right ventricular pressure did not exceed the systemic pressure, and the pressure curve in the pulmonary artery retained its arterial contour. In one case which came to autopsy, the leaflets of the pulmonic valve were only partially fused causing a moderate reduction of the valvular opening.

The authors conclude that in cases of this type corrective surgery is not indicated because the functional capacity of the patient is good and valvulotomy may damage the valves instead of improving their function.

PICK

Gordon, A. J., Lasser, R. P., Moscovitz, H. L., Brahms, S. A., and King, F. H.: The Diagnosis of Overriding Aorta. With Special Reference to Circulation Time Tests. Am. J. Med. **15:** 158 (Aug.), 1953.

After reviewing the methods designed to establish the presence of overriding aorta in congenital heart disease, the authors conclude that passage of a catheter into the aorta from the right ventricle is undoubtedly the most reliable method of proving the diagnosis of overriding aorta. A rapid right ventricle-to-ear circulation time is strongly in favor of the existence of this anomaly. With rare exceptions the presence of a right-sided aortic arch in a cyanotic patient indicates that the aorta arises in whole or in part from the right ventricle. Conventional studies involving the speed of the circulation, including angiocardiography, may prove a right-to-left shunt without indicating its site. Pressure relationships obtained during cardiac catheterization may be relied upon only to exclude overriding aorta.

HARRIS

Morse, M., and Cassels, D. E.: Arterial Blood Gases and Acid-Base Balance in Cyanotic Congenital Heart Disease. J. Clin. Invest. **32:** 837 (Sept.), 1953.

In a large group of children with various forms of congenital heart disease it was found that the great majority have a normal or higher than normal arterial oxygen content. This is due to the fact that many have a high HbO_2 capacity. Deviations of the acid-base characteristics from normal were found to be due in most cases either to fixed acid excess or to a combination of fixed acid excess and carbon dioxide deficit.

WAIFE

Tosetti, R., Actis Dato, A., and Angelino, P. F.: Histopathology of Small Pulmonary Vessels in Congenital Stenosis of the Pulmonary Artery. Arch. mal. coeur **46:** 780 (Sept.), 1953.

In seven cases with various types of pulmonic stenosis the authors studied the histologic appearance of pulmonary arterioles and venules less than 1 mm. in size. In two cases the vessels showed a normal structure and in five the vessel wall was markedly atrophic so that the histologic distinction between an arteriole and venule became impossible. Evidence of vasoconstriction or of thickening of the intimal layer was found nowhere. Intravascular thrombi in various stages of organization were common findings. In one case, a tetralogy, an angiomatous pattern of the vessels could be demonstrated, possibly related to the development of collateral bronchial circulation. Application of the index of Kernohan (the ratio of thickness of vessel wall to diameter of its lumen) revealed, as a rule, values far exceeding those found in mitral disease, and approaching values found in conditions with increased pulmonary flow. It would appear that the abnormalities of the small pulmonary vessels in pulmonic stenosis are not the consequence of the altered pulmonary hemodynamics, but rather represent an associated congenital vessel anomaly.

PICK

Puech, P., Esclavissat, M., and Lasson, R. L.: Interauricular Communication. A Study of 50 Cases. Arch. mal. coeur **46:** 798 (Sept.), 1953.

Fifty cases with proven atrial septal defects were analyzed in an attempt to establish a correlation between clinical data, radiologic and electrocardiographic findings, and the results of hemodynamic investigations.

Clinically dyspnea is found predominantly with venoarterial or bidirectional shunts, and when the pulmonary arterial pressure is considerably elevated. Under the latter circumstances systolic and diastolic murmurs in the pulmonic area become very pronounced. Heart failure occurs mainly in older individuals, and in Lutembacher's syndrome.

Roentgenologic cardiomegaly is seen particularly in the presence of bidirectional shunts and in Lutembacher's disease. Although there is no definite correlation of the size of the pulmonary arterial segment and the degree of pulmonary hypertension, aneurysmal dilatation of the pulmonary artery is invariably associated with severe pressure elevation within the vessel.

In about a fourth of the cases the P-R is prolonged and the P wave has an abnormal contour. The latter is almost always associated with pressure elevation in the right atrium or ventricle. In 86 per

cent of the cases right bundle branch block, usually of the incomplete type, was found. With marked pulmonary hypertension, signs of right heart strain appear in the electrocardiogram, with or without evidence of impairment of intraventricular conduction. "Ischemic alterations" of the T wave may be seen over the right precordium.

The authors conclude that in cases with interatrial communications those with severe pulmonary hypertension represent a particular group with regard to the modified clinical picture, the particular conditions of hemodynamics, and the diagnostic problems which may arise.

PICK

Clowes, G. H. A., Jr., Hackel, D. B., Mueller, R. P., and Gillespie, D. G.: Relationship of Pulmonary Functional and Pathological Changes in Mitral Stenosis. Arch. Surg. **67:** 244 (Aug.), 1953.

Sixteen patients underwent commissurotomy for mitral stenosis. The disability classification was: grade II in 1 patient, grade III in 11 patients and grade IV in 4 patients. Methods of study included lung biopsy, cardiac catheterization, measurements of pulmonary function and finally, clinical estimates of the improvement for periods up to one year.

Definite thickening of the arteriolar walls with intimal proliferation was found in all but one of the lungs. The degree of sclerosis was expressed as a lumen-to-wall ratio. These ratios did not correlate with either the pulmonary arterial pressures or the calculated pulmonary arteriolar resistances, but did show a significant correlation with the product of pulmonary arterial pressure times the duration of symptoms. As a result of these determinations the authors suggest that the age of the patient and the height and duration of the elevated pulmonary pressure are all important in the production of pulmonary arteriolar sclerosis.

The clinical results of mitral commissurotomy were in general good, although patients with severe pulmonary arteriolar sclerosis may take six months or longer to obtain maximum benefit. Poor results appear not to be caused by the state of the pulmonary vasculature but by factors within the heart such as concomitant valvular disease or myocarditis which interfere with normal cardiac function.

WESSLER

Van Buchem, F. S. P., Homan, B. P. A. A., Dingemanse, E., and Huin in't Veld, L. G.: Endocrine Disturbances in Coarctation of the Aorta. Acta med. Scandinav. **143:** 399 (Fasc. 6), 1952.

This report is concerned with observations made in 11 patients with coarctation of the aorta. Two of the three female patients showed features of the syndrome of Turner, including retarded growth, absence of axillary and pubic hair, amenorrhea, slight development of the sex organs and hypoplasia or absence of the ovaries. Congenital anomalies such as pterygium colli and cubitus valgus are common in this condition. The excretion of gonadotropin was increased in one of the patients with the Turner syndrome. Of the eight male patients with coarctation of the aorta, five showed delayed puberty while the others were normal in this respect. In the majority of the males the excretion of 17-ketosteroid IV was lower than the average normal value suggesting subnormal testosterone production. On the other hand the metabolites of the suprarenal cortical hormones were present in relatively large amounts in these same patients. It is mentioned that if clear-cut endocrine disturbances are present it seems that one has to reckon with a less favorable condition of the myocardium and blood vessels which may aggravate the risk of surgical correction for coarctation of the aorta. Furthermore, if there are signs suggesting agenesis of the ovary, it may be well to treat the patient with estrogenic substances prior to surgery.

ROSENBAUM

CORONARY ARTERY DISEASE

Oliver, M. F., and Boyd, G. S.: The Clearing by Heparin of Alimentary Lipemia in Coronary Artery Disease. Clin. Sc. **12:** 293 (Aug.), 1953.

One hundred subjects were investigated, 50 with definite coronary artery disease and 50 hospital controls. Plasma turbidity was estimated by optical densitometry after a standard meal containing 100 Gm. of fat. Heparin, 0.3 mg., was given intravenously 3 hours after the meal, and clearing determined at 15 and 90 minute intervals.

It was found that 31 per cent of the lipemia was cleared in the coronary group as compared with 64 per cent in the controls. Statistically the differences were found to be highly significant for the males and somewhat less so for the females. Two thirds of the clearing had already occurred within one and one-half minutes of injection. There was no correlation in either main group with age, levels of cholesterol or cholesterol esters, or plasma phospholipids. There was a slight overlap in both groups.

A complete explanation of the phenomenon of chylolytic action of heparin is still lacking. Various hypotheses are discussed. It is probable that heparin in some way modifies the physical state of plasma fat, perhaps by altering surface tension or in other ways. It is conceivable that arteriosclerotic changes are associated with diminished availability of an endogenous heparin-like substance, thereby reducing a circulating chylolytic factor.

ENSELBERG

Linden, L.: Prognostic Aspects of Myocardial Infarction. Acta med. scandinav. **143:** 464 (Fasc. 6), 1952.

This report is based upon observations made in 506 patients studied at the University Hospital

Upsala, over a 10-year period. The mortality rate was 45.5 per cent. The mortality was observed to increase with age, with recurrent infarction especially after a brief interval, with blood sugar levels exceeding 150 mg. per 100 ml., with elevation of the nonprotein nitrogen and with involvement of the septum. Treatment with dicumarol reduced the incidence of thromboembolic complications from 5 to 2.5 per cent, and reduced the mortality from 30 to 30.5 per cent, not including the deaths which occurred within three days of the onset of the infarction. The mortality was 100 per cent in 11 diabetic men and 80 per cent in 20 diabetic woman.

ROSENBAUM

De Langen, C. D.: The Pressure Gradient in the Arterial Wall and the Problem of Arteriosclerosis. Cardiologia **22**: 315 (Fasc. 5), 1953.

The author calls attention to the problem of pressure differences in the various layers of the arterial wall. There must be a pressure gradient present between the intravascular pressure and that which equals the pressure in the tissues surrounding an artery, otherwise the vessel would dilate until the two pressures are equalized. With the acceptance of such a gradient, it is difficult to conceive a movement of lipids from the capillaries to the arterial lumen, however, it is easier to understand that the lipids wander in the opposite direction—from the lumen into the different parts of the arterial wall. This can explain the fact that the intima and inner part of the media are predisposed sides for precipitation of fatty substances. The concept presented is of importance for a better understanding of the different types of arteriosclerosis.

PICK

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY AND BALLISTOCARDIOGRAPHY

Markham, J. D., and Hoff, E. C.: Toxic Manifestations in the Antabuse-Alcohol Reaction. J.A.M.A. **152**: 1597 (Aug. 22), 1953.

The scope of this report is limited to an analysis of the electrocardiographic changes occurring during the tetraethylthiuramdisulfide–alcohol reaction, made at intervals during such reactions on 44 patients, representing 221 electrocardiograms. Definite changes were observed in 91 per cent of the 44 patients. The principal changes were lowering, flattening, or inversion of T waves; S-T segment depression in one or more leads; and prolongation of the Q-T interval. The pattern of changes is the same as that seen in ventricular strain (mainly right). The pattern of acute coronary insufficiency has not been observed. There is strong evidence that some of the changes are due to a direct toxic effect on the myocardium. The effect is reversible with recovery from the reaction and with response to the administration of ascorbic acid, but apparently does not respond to oxygen administration. Such changes in the electrocardiogram indicate that tetraethylthiuramdisulfide should be withheld if there is any suspicion of cardiac abnormality.

KITCHELL

Richards, A. G., Simonson, E., and Visscher, M. B.: Electrocardiogram and Phonogram of Adult and Newborn Mice in Normal Conditions and under the Effect of Cooling, Hypoxia and Potassium. Am. J. Physiol. **174**: 293 (Aug.), 1953.

There is no distinct T wave although the terminal QRS segment is notched. Bradycardia of cooling or hypoxia separates the notch into a definite wave without a distinct S-T segment. Potassium increased notch amplitude. The authors assume that depolarization and repolarization overlap due to the short duration of excitation. K_{Q-T} values fall far outside the human range. First heart sounds occur in adult mice 0.015 second after the onset of QRS. The second sound is found just before the start of P.

OPPENHEIMER

Donzelot, E., Milanovich, J. B., Heim de Balsac, R., Doliopoulos, Th., and Roger, R.: Comparative Study of 100 Normal Ballistocardiograms Obtained by Piezoelectric and Photoelectric Systems. Arch. mal. coeur **46**: 746 (Aug.), 1953.

A ballistocardiographic system consists of a series of elements—the heart, the arteries, the body, and the table—each of which has its particular characteristics of oscillation. A curve obtained by such a system represents the algebraic sum of a variety of oscillations, and its final contour is determined by interference, resonance, superposition and mutual extinction of waves of various origin. Most of these waves, however, have a similar range of frequency (5 to 6 cycles per second).

At the present time, interpretation of clinical tracings must be based purely on empiric grounds. Both piezoelectric and photoelectric curves are displacement curves and are therefore similar in contour but differ in the size of their amplitude. Even with reduction of the standardization to one half, piezoelectric curves are about 3.5 times larger than photoelectric recordings. Normally H is the smallest and J the largest of the systolic deflections, while K equals or exceeds the I wave. Among the diastolic waves L is the largest and M, N, and O become progressively smaller. In fact, N and O may be absent under normal conditions. From the clinical standpoint the evaluation of the amplitude of IJ is most important. However, respiratory variations do occur, and must always be taken into consideration.

PICK

Doll, E., Klepzig, H., Reindell, H., and Mehnert, G.: The Precordial Electrocardiogram in the Child. Ztschr. Kreislaufforsch. **42**: 641 (Fasc. 17/18), 1953.

The authors studied the contour of the normal precordial electrocardiogram (leads V_1 to V_6) in 150 healthy children of various ages (5 weeks to 15 years), and its gradual transformation from the pattern characteristic of the infant to that of adolescence. All data were submitted to vectorial analysis. Normal ranges of the size of the R wave in each of the six precordial leads were tabulated for five age groups.

The R/S ratio in right sided chest leads is greater than 1 in the youngest and decreases proportionately with increasing age. The timing of the intrinsicoid deflection, however, remains unchanged in these leads, whereas it shows a slight and progressive delay in leads V_5 and V_6 as the child becomes older. In infants and small children negativity of T wave may extend from V_1 to V_4. The incidence of negative or diphasic T waves in these leads then decreases in proportion to the advancing age.

PICK

Master, A. M., Donoso, E., Pordy, L., and Chesky, K.: The Ballistocardiogram in Peripheral Vascular Disease. Am. Heart J. **46**: 180 (Aug.), 1953.

The authors present the ballistocardiographic findings in 65 cases with peripheral vascular disease, including 36 cases with uncomplicated arteriosclerotic peripheral vascular disease and uncomplicated thromboangiitis obliterans, recorded by means of the Pordy dual displacement and velocity apparatus. Of 22 patients under 50 years with uncomplicated arteriosclerotic peripheral vascular disease, 18 presented abnormal ballistocardiograms at rest. In 2 cases, the tracing was borderline. Of 14 patients under 50 years of age with uncomplicated thromboangiitis obliterans, 10 had abnormal resting ballistocardiograms. In one case, the tracing was borderline. In all cases of peripheral vascular disease, complicated by cardiac involvement, the resting ballistocardiograms were abnormal. The majority of patients under fifty years of age with uncomplicated peripheral vascular disease have an abnormal ballistocardiogram.

RINZLER

Biber, D., and Schwartz, M. L.: Some Limitations of Vectorcardiography. Am. Heart J. **46**: 161 (Aug.), 1953.

The frontal plane vectorcardiogram derived from leads I and aV_f of a case presented by the authors showed ventricular complexes which resembled fairly closely the corresponding complexes of the electrocardiogram. When lead PA (the posterior-anterior lead which is taken at the level of the tenth thoracic vertebra with one electrode at the right posterior axillary line and the other at the right anterior axillary line, and which has polarity such that relative positivity at the anterior electrode produced an upward deflection) was combined with lead I to derive the horizontal plane vectorcardiogram and the precordial complexes derived from the loops, it was revealed that these ventricular precordial complexes differed from those taken directly from the patient.

Because in some individuals the horizontal plane vectorcardiogram may fail to reflect changes which are recorded by the precordial leads of the electrocardiogram, the authors conclude that the usefulness of the vectorcardiogram is limited and may not equal that of the conventional electrocardiogram.

RINZLER

Helm, R. A., and Fowler, N. O., Jr.: Studies on the QRS-T Angle. Am. Heart J. **46**: 229 (Aug.), 1953.

This report deals with studies relating to the determination of the angle between certain spatial QRS and T vectors and the angles between their planar projections. A trigonometric method is used for the calculation of the angle between any two spatial vectors, given the angular positions of their projections on two mutually perpendicular planes. An appendix gives the necessary formulas and their derivations.

The determination of the angles between the mean QRS and T vectors from 12 lead electrocardiograms of 20 normal individuals, 18 to 57 years of age, suggests that the upper limit of normal previously given for this determination is too low. Statistical study of the vectorcardiographic data indicates that there was a significant difference in the mean of the angles between the largest spatial and frontal QRS and T vectors obtained with the cube and tetrahedral reference frames. A significant association, as determined by regression, could not be demonstrated for either the spatial or the two planar angles obtained with these two systems. While these findings do not prove conclusively that a significant association might not exist if more cases were studied, it suggests that there would be difficulty in translating from one system to another in a given patient.

RINZLER

Walker, R. P., Reeves, T. J., Willis, K., Christianson, L., Pierce, J. R., and Kahn, D.: The Effect of Surface and Recording Technique on the Direct Ballistocardiogram. Am. Heart J. **46**: 166 (Aug.), 1953.

The effect of various surfaces on the direct ballistocardiogram were studied. It was found that hard, flat surfaces were less desirable than one of relatively nonelastic material which fitted the contour of the body. The evidence for this was as follows: In certain healthy, young men, grossly

abnormal patterns were observed on the table and floor, but became normal with the subject in sand or putty. Alterations in the area of contact between the back and the table made by alterations of the positions of the arms resulted in well-marked changes in the ballistocardiogram; these changes were not observed in sand or putty. Cadaver experiments showed a quicker return of body oscillations to the base line, following a standard tap, with an increased vibratory frequency, in some cadavers at least, in the sand and putty as compared to the table and floor. Minor changes in footrest, headrest, etc., caused changes in tracings made on the table.

In the study of the recording apparatus, the authors found that the commercial coil-magnet system using a 25 microfarad capacitor records a mixture of velocity and displacement. However, if physiologic correlation is sought, this might not be desirable. The bellows with air-conduction system to a piezoelectric crystal was satisfactory.

RINZLER

Souliè, P., Di Matteo, J., Voci, G., and Barbano, G.: Electrocardiogram and Mitral Insufficiency. Arch. mal. coeur **46**: 769 (Sept.), 1953.

In 30 cases of mitral regurgitation (six confirmed during mitral surgery, eight by autopsy, and the rest diagnosed on clinical grounds) the electrocardiographic findings were correlated with hemodynamic, roentgenologic and anatomic findings. The material was divided into two groups according to presence or absence of concomitant mitral stenosis. Cases complicated by aortic valvular lesions or systemic hypertension were excluded.

Three types of electrocardiograms were found, one characteristic for left heart strain in an electrically vertical position, a second characteristic for combined heart strain, and a third which was normal in every respect. The type of the electrocardiographic alteration depends on the dynamic importance of the regurgitation relative to the stenosis present. The pattern of combined heart strain may develop in pure mitral insufficiency when the latter leads to anatomic alteration of the pulmonary vessels and thus to the development of pulmonary hypertension. A normal electrocardiogram does not rule against a significant mitral lesion. It can be found in the presence of marked pressure elevation in the pulmonary artery and apparently is the result of "compensated" (balanced) biventricular strain.

PICK

Wenger, R., and Doneff, D.: Vectorcardiographic Studies in Myocardial Infarction. Cardiologia **22**: 303 (Fasc. 5), 1953.

Vectorcardiograms recorded according to the method of Polzer and Schuhfried in 50 cases of myocardial infarction, some with autopsy control, are reported, and patterns typical for various localizations of infarction are illustrated. The observed abnormalities of the QRS loop consisted in a change of the spatial location of the entire loop, in a change from a normally clockwise to a counterclockwise direction especially in the frontal plane, and in marked distortions of the loop contour by abnormal buckles and notchings.

Vectorcardiographic analysis permits the separation, in posterior wall infarction, of a group with more apical (diaphragmatic) location from a rarer group with strictly posterior (basal) infarction. In the former, there is a greater tendency of the initial portion of the frontal loop to deviate upwards and to the left, and to take a counterclockwise direction. Although there was no case where the vectorcardiogram would reveal myocardial infarct not recognizable in a standard electrocardiogram, the authors believe that vectorcardiography is of diagnostic value, especially in cases with equivocal alterations of the conventional electrocardiogram.

PICK

HYPERTENSION

Ford, R. V., Moyer, J. H., and Spurr, C. L.: The Effect of Posture and Adrenergic Blockade with Dibenzyline on Renal Hemodynamics and Excretion of Water and Electrolytes in Patients with Hypertension with and without Renal Damage. Am. Heart J. **46**: 268 (Aug.), 1953.

The effects on renal hemodynamics of oral Dibenzyline sufficient to induce adrenergic blockade were studied in 12 patients with hypertension with and without renal disease, by measurements of glomerular filtration rate (inulin clearance), renal plasma flow (para-aminohippurate clearance), and maximum tubular excretory capacity. The rates of urine formation, sodium excretion, potassium excretion, and changes in blood pressure were observed. The effects on renal hemodynamics were observed in both the recumbent as well as the tilted position.

In the recumbent position, adrenergic blockade produced a reduction in blood pressure without alteration in renal function. In the tilted position, the reduction in renal function was the same before and after adrenergic blockade. These changes were not related to the degree of renal impairment as measured by glomerular filtration rate.

These results suggest renal autonomous adjustment to decreased filtration pressure, independent of autonomic control or else a specific resistance of the kidney to adrenergic blockade.

The excretion of water and electrolytes in patients with hypertension and associated renal damage is depressed out of proportion to renal blood flow and glomerular filtration rate. This indicates that the effect of tilt on electrolyte excretion in the hypertensive patient is qualitatively similar to the nor-

motensive subject without renal damage and is not affected by adrenergic blockade with Dibenzyline.

RINZLER

Ruskin, A: Drastic Sodium Depletion in the Treatment of Essential Hypertension. Texas State J. Med. **48:** 583 (Aug.), 1952.

Drastic sodium depletion accomplished by a 200 mg. sodium diet plus mercurial diuretics twice weekly caused decreases of more than 10 mm. of mercury in the diastolic blood pressure in 27 of 46 patients with benign essential hypertension. Statistically significant hypotensive effects resulted in about three-quarters of the cases. The hypotensive action was accompanied by weight loss, fall in serum sodium levels, and occasionally, mild manifestations of the low salt syndrome.

BERNSTEIN

Von Euler, U. S., Lund, A., Olsson, A., and Sandblom, P. H.: Noradrenaline and Adrenaline in Blood and Urine in a Case of Pheochromocytoma. Scandinav. J. Clin. & Lab. Invest. **5:** 122 (No. 2), 1953.

This report is concerned with a man aged 23 years who was found to have a pheochromocytoma the size of a hen's egg located anteromedial to the hilus of the left kidney. Sustained elevation of the systolic and diastolic blood pressures had suggested essential hypertension but an elevated basal metabolic rate, a hyperglycemic response to the glucose tolerance test, sweating, eosinopenia and fatigue were considered suggestive of pheochromocytoma. This diagnosis was not sustained by x-ray investigation nor by the responses to tetraethylammonium or Regitin. Measurement of the urinary catechol excretion disclosed definitely increased levels (1010–2400 μg. noradrenaline and 16–19 μg. adrenaline per 24 hour period). Simultaneous measurements showed an average blood level of 3.6 μg. per 100 ml. noradrenaline and a corresponding urinary output of 110 per μg. per hour. After operation the urinary excretion became 1.5 μg. adrenaline and 34 μg. noradrenaline per 24-hour period and the catechol level in the blood was less than 0.2 μg. per 100 ml. The tumor weighed 40 Gm.; it showed 590 μg. per Gm. noradrenaline and 12 μg. per Gm. adrenaline.

ROSENBAUM

Jeffers, W. A., Zintel, H. A., Hafkenschiel, J. H., Hills, A. G., Sellers, A. M., and Wolferth, C. C.: The Clinical Course, Following Adrenal Resection and Sympathectomy, of 82 Patients with Severe Hypertension. Ann. Int. Med. **39:** 254 (Aug.), 1953.

Eighty-two severely hypertensive patients have been treated with various degrees of adrenal resection with and without the limited Adson sympathectomy or the more extensive Smithwick thoracolumbar sympathectomy. After a postoperative period varying between 1 and 33 months, it has been observed that 23 per cent have shown an excellent response; in 14 per cent the response was fair; in 32 per cent the results were poor. Twenty-one per cent have failed to survive. Only one has died from uncomplicated adrenal insufficiency. The usual cause of death has been a stroke or a coronary occlusion. Paroxysmal dyspnea or congestive heart failure have been strikingly benefited, even to the point of eliminating the need for digitalis. This appears to be primarily the result of extensive resections of adrenal cortex. The majority of those subjected either to total or subtotal adrenalectomy have required adrenal cortical replacement therapy postoperatively. The indications for operation include three features: (a) an average diastolic blood pressure of 120 mm. of mercury or more; (b) a failure to respond to intensive medical therapy; (c) evidences of progressive vascular damage. Tentative contraindications include any of the following: (a) poor renal function, with excretion of less than 20 per cent of phenolsulfonphthalein 15 minutes after intravenous injection and/or a blood urea nitrogen of over 20 mg. per cent; (b) convalescence from a stroke or coronary occlusion for less than 6 months; (c) age of 55 years or more; (d) inability for any reason to cooperate in taking adrenal cortical replacement therapy. The hazard of acute adrenal insufficiency after operation constitutes an ever present threat, particularly during the summer months. The early symptoms of this syndrome must be recognized immediately and treated promptly in order to prevent an unfortunate outcome. For this reason, this operative procedure should be performed only when a highly integrated team of specialists is available to deal with any emergency.

WENDKOS

Smithwick R. H., and Thompson, J. E.: Splanchnicectomy for Essential Hypertension. J.A.M.A. **152:** 1501 (Aug. 15), 1953.

These authors outline a method of classifying hypertensive patients depending on level of blood pressure and amount of cardiovascular disease present. Mortalities and survival rates for 1,266 hypertensives treated by thoracolumbar splanchnicectomy and for 467 medically treated control patients are compared. Superior results were had following surgery in all four groups, but best results were obtained in patients who fell into groups 2 and 3. Patients should be operated upon before they fall into group 4 as the eventual mortality for this group is high regardless of the therapy employed. The authors' present method of selection of therapy for hypertensive patients is outlined and is based on the known effect of surgical treatment on prognosis.

KITCHELL

Moser, M., Syner, J., Malitz, S., and Mattingly, T. W.: Acute Psychosis as a Complication of Hydralazine Therapy in Essential Hypertension. J.A.M.A. **152:** 1329 (Aug. 1), 1953.

A case of acute psychosis as a result of hydralazine (Apresoline) overdosage in a patient with essential hypertension is reported. This episode was not related to change in blood pressure or renal function. Clinical recovery followed in 12 to 24 hours after withdrawal of the drug. The fact that there was a subsequent severe prolonged depression that was unrelated to hydralazine therapy suggests that the episode may have resulted from a release of basic personality conflicts after the disease stage had been altered by the drug. It is suggested that administration of Apresoline as well as of other agents used in the treatment of hypertension should be discontinued or the dose reduced if personality changes occur.

KITCHELL

Reynolds, T. B., Paton, A., Freeman, M., Howard, F., and Sherlock, S.: The Effect of Hexamethonium Bromide on Splanchnic Blood Flow, Oxygen Consumption, and Glucose Output in Man. J. Clin. Invest. **32:** 793 (Sept.), 1953.

There is little information concerning splanchnic blood flow after the administration of hexamethonium. The authors studied seventeen patients without evidence of hepatic dysfunction or disturbance of carbohydrate metabolism. Five had essential hypertension. The splanchnic blood flow was estimated by infusing Bromsulphalein and determining hepatic extraction, and by measuring the arterial and hepatic vein concentrations. It was found that in fifteen of the seventeen subjects splanchnic blood flow fell in proportion to the fall in arterial pressure. There was no change in the vascular resistance of the splanchnic area, thus indicating no splanchnic vasodilatation. There was no significant alteration in splanchnic oxygen consumption, glucose output from the liver, and arterial glucose and lactic acid concentrations. In two subjects, splanchnic blood flow rose and there was a fall in vascular resistance. In short, there was no over-all change in the capacity of the splanchnic vascular bed and it also appears that the fall in blood flow leads to a fall in portal venous pressure without changing the vascular resistance.

WAIFE

Green, D. M.: Experimental Hypertension. Ann. Int. Med. **39:** 333 (Aug.), 1953.

The available data indicate that all forms of hypertension involve both nervous and humoral pressor mechanisms to some extent, although neurogenic hypertension is predominantly nervous in origin and renal hypertension predominantly humoral. Both elements are intermixed in post-desoxycorticosterone acetate and essential hypertension to degrees which appear to vary from one animal or human subject to another.

Of all the varieties of experimental hypertension, the post-desoxycorticosterone acetate syndrome most closely resembles the human disease in its functional as well as in its anatomic aspects. It is notable that no other types of hypertension are as independent of the presence of the adrenal cortex for the continued maintenance of elevated blood pressure.

Of potential significance for the treatment of the human patient is the resistance of post-desoxycorticosterone acetate hypertension to all therapeutic efforts, with the sole exception of hypophysectomy. If this experimental disease is analogous to essential hypertension, the intensive study of the hypophysis and related hypothalamic areas becomes of singular importance.

WENDKOS

Ullman, T. D., and Diengott, D.: Effect of Hexamethonium on Renal Hemodynamics in Man. Arch. Int. Med. **92:** 228 (Aug.), 1953.

The effect of intravenously injected hexamethonium on the urine flow, glomerular filtration rate, renal plasma flow and effective renal blood flow, filtration fraction, and calculated renal resistances was studied in two nonhypertensive and 10 hypertensive subjects. Hexamethonium caused marked reduction in urine flow and moderate to marked decrease in glomerular filtration rate. Renal plasma flow and effective renal blood flow were elevated in more than half of the observations and decreased in the remaining ones. The filtration fraction was markedly lowered in all observations. The renal vascular resistances generally were markedly decreased, but showed an increase in some observations. The changes in renal resistances affected all parts of the renal vascular tree about equally.

The decrease in renal plasma flow and the increase in renal vascular resistance, when observed in periods immediately following the administration of the drug, may be a result of transitory activation of a sympatheticomimetic mechanism by the ganglion-blocking agent. These results and other data reported in the literature do not indicate a detrimental influence of the drug on the kidney. Overdosage of the drug, leading to a too sudden and too prolonged reduction in urine flow, should however, be avoided.

BERNSTEIN

PATHOLOGIC PHYSIOLOGY

Howarth, S.: Cardiac Output in Osteitis Deformans. Clin. Sc. **12:** 271 (Aug.), 1953.

Thirteen cases of Paget's disease were studied, including one in which the disease process was inactive. In this patient, the cardiac output was normal. In five active cases, the resting cardiac

output was increased (7.2 to 13.3 L. per minute). In general, the cardiac output was not abnormally elevated in those cases with alkaline phosphatase levels below 45 K-A units per 100 cc., or in those cases with less than 35 per cent involvement of the skeleton by active disease.

The author emphasizes that the occurrence of increased cardiac output in cases of generalized active osteitis deformans is not uncommon. It may be difficult to recognize the high output clinically. The finding of a high phosphatase level does not necessarily imply an associated rise in cardiac output. The extent of skeletal involvement is of at least equal importance in this regard. It is to be borne in mind that an increase in heart size or left ventricular hypertrophy may be a consequence of the high output.

ENSELBERG

Cassels, D. E., and Morse, M.: Arterial Blood Gases and Acid-Base Balance in Normal Children. J. Clin. Invest., **32**: 824 (Sept.), 1953.

Data have been collected dealing with blood gases, oxygen saturation, and acid-base balance in a study of one group of 41 children of both sexes, age 2 to 10 years, another group of 63 boys 11 to 17 years of age, and a number of normal young male adults. Among the findings was the fact that the hemoglobin concentration of the blood increases with age from 12.3 Gm. at age two to 15.8 Gm. per 100 ml. in the adult. In very young children the mean per cent arterial oxygen saturation and the carbon dioxide content of the blood are lower than in the older children and adults. In the 2 and 3 year age group, displacement of acid-base balance from the adult pattern is entirely in the direction of fixed acid excess or metabolic acidosis. Between the ages of 4 and 11, there appears to be a slight acid excess and carbon dioxide deficit. Above the age of 12, the acid-base pattern is shifted toward a slight carbon dioxide excess.

Although available data agree that the alkali reserve of the blood is low in the very young child, and the adult level is not reached until about twelve years or later, a satisfactory explanation must await further experimentation.

WAIFE

McGregor, M., Bothwell, T. H., Zion, M. M., and Bradlow, B. A.: The Effects of Oxygen Breathing on the Pulmonary Circulation in Mitral Stenosis. Am. Heart J. **46**: 187 (Aug.), 1953.

The effects of breathing high concentrations of oxygen on the pulmonary hypertension found in mitral stenosis were studied in 13 patients, in 12 of whom the principal lesion was considered to be the stenosis and in one, mitral regurgitation. The administration of pure oxygen resulted in a fall in the raised pulmonary artery pressure in all instances and a significant fall in total pulmonary resistance in 10 instances. There was no correlation between initial arterial anoxia that was present in nine patients and the fall in pulmonary resistance following oxygen. In spite of this, the authors feel that local anoxia caused by pulmonary congestion and edema may at least play some part in the development of pulmonary hypertension in mitral stenosis.

RINZLER

Deuchar, D. C., and Venner, A.: The Blood Pressure During Cardiac Massage in Man. Brit. M. J. **2**: 134 (Aug. 1), 1953.

The recording of intra-arterial blood pressure during surgical operations by means of an electrical condenser manometer and a fine plastic catheter provided opportunity for recording pressures during cardiac massage after the onset of ventricular fibrillation in one case and very feeble cardiac action in another. In the first case a blood pressure of 55/20 mm. Hg was attained and in the second, one of 70–75/30. The pulse waves were of a slowly rising plateau configuration.

MCKUSICK

Kishine, T., Igarashi K., Tsukamoto, H., Suto, K., and Watanabe, Y.: A Method of Simultaneous Estimation of Effective Renal Blood Flow and Circulating Blood Volume by Sodium Para-aminohippurate. Tohoku J. Exper. Med. **3**: 275 (Aug.), 1953.

The authors describe their method of simultaneous estimation of effective renal blood flow and circulating blood volume in the normal human body by para-aminohippurate, and also demonstrate that the amount of para-aminohippurate which penetrates into tissue cells can be calculated in the course of the estimation. As para-aminohippurate concentration in plasma and extracellular fluid is perhaps equal in para-aminohippurate equilibrium, they discuss at the same time the probability of calculating the volume of extracellular fluid by ascertaining it in their study.

BERNSTEIN

Berlin, N. I., Goetsch, C., Hyde, G. M., and Parsons, R. J.: The Blood Volume in Pregnancy as Determined by P^{32} Labeled Red Blood Cells. Surg., Gynec. & Obst. **97**: 173 (Aug.), 1953.

Using P^{32} labeled red blood cells, the blood volume was determined in 157 pregnant patients and 34 postpartum patients. The study demonstrated that there was an initial drop in total red blood cell volume of approximately 200 cc. during the first two months, followed by a progressive rise to a peak in the ninth month. At the latter period the volume was 270 cc. above the normal nonpregnant value. During the last month before delivery there was a decrease of 170 cc., with a further reduction of 300 cc. during delivery and in the immediate postpartum period.

The plasma volume showed a progressive increase

beginning with the first month of pregnancy and reaching a peak in the ninth month of approximately 1200 cc. above the normal volume. In the period prior to delivery and in the postpartum state, there was a significant drop in volume. From the data, it was felt that a true anemia existed in the first and second trimesters of pregnancy.

ABRAMSON

Cabrera, E., and Friedland, C.: The Wave of Ventricular Activation in Left Bundle Branch Block with Infarction. (A New Electrocardiographic Sign). Arch. Inst. cardiol. Mexico, **23:** 441 (Aug. 31), 1953.

The authors study 45 cases of left bundle branch block and describe a new electrocardiographic sign which appears only in those cases which are complicated by anteroseptal infarction. This sign consists of a small notch, lasting 0.05 second or more in the terminal part of QRS. It is present only in those chest leads which have a rS or a QS type—usually V_3 and V_4. This sign was found in 91 per cent of the cases with infarction and in 6 to 9 per cent of those without infarction.

The authors discuss the possibility that a focal block or an inactive area of the septum may cause this notch.

LUISADA

Tyrer, J. H.: A Comparison of the Direct Peripheral Actions upon Systemic Venous Pressure of k-Strophanthosid, Digoxin and Ouabain. Quart. J. Exper. Physiol. **38:** 177 (Aug.), 1953.

Therapeutic doses of digoxin, k-strophanthosid and ouabain were given intravenously to sheep whose hearts had been replaced functionally by a double perfusion pump and whose pulmonary and systemic circulations were perfused at constant rates. These glycosides increased mean inferior vena caval, mean superior vena caval and mean hepatic venous pressures; in sheep with intact circulations, however, they caused no significant alteration of systemic venous pressure. Since any cardiac effects were excluded by the constant perfusion, it was concluded that the glycosides have a direct constrictive action on the systemic veins. The direct action on venous pressure is probably not the principal action of these drugs, but should be considered in interpreting the many effects of digitalis in the intact animal.

MAXWELL

Obrink, K. J., and Essex, J. E.: Chronotropic Effects of Vagal Stimulation and Acetylcholine on Certain Mammalian Hearts with Special Reference to the Mechanism of Vagal Escape. Am. J. Physiol. **174:** 321 (Aug.), 1953.

Recovery is rapid after vagal stimulation in guinea pigs, rabbits and dogs. The vagi liberate acetylcholine at a constant rate for a duration of stimulation that exceeded the time for vagal escape. Repeated stimulation of the vagi remained effective in dogs but was easily exhausted in some guinea pigs. In these latter cases eserine, epinephrine or norepinephrine restored the response. Vagal stimulation would bring the heart to a standstill, but acetylcholine would not. The authors suggest that this difference may depend upon intracellular vagal endings as compared with injected acetylcholine which must penetrate from without. Using radiosodium it was shown that the sinoatrial node has a higher concentration of sodium than surrounding tissues. When the vagus was stimulated this difference became less. This disappearance of the difference between node and surrounding tissue was thought to be a sign of a simultaneous decrease of the high sensitivity of the node to acetylcholine.

OPPENHEIMER

Radner, S.: Method for Recording Aortic Pressure Pulses. Scandinav. J. Clin. & Lab. Invest. **5:** 129 (no. 2), 1953.

A method is described for the recording of aortic pressure pulses through a needle introduced into the arch of the aorta percutaneously from the suprasternal notch in the neck. The needle used has an outer diameter of 0.9 mm. and an inner diameter of 0.5 mm. It is mounted on a three-way stopcock and supported by a closely fitting cylinder which surrounds its proximal 4 cm. The free distal length of the needle is 10 cm. A stilette is in place until the aorta is punctured. The needle is then connected with a Tybjaerg Hansen manometer by means of a canalized knob and a short Cournand catheter. An infusion of saline-heparin solution is maintained through the needle when recordings are not being taken. The puncture is done with the patient supine, with fluoroscopic control and local anaesthesia. Vigorous pulsations are said to be felt with the needle, usually at a depth of 4 to 7 cm. but when the tip of the needle has been inserted through the aortic wall these vigorous pulsations are no longer palpable. The number of cases in which the procedure has been applied is not given, but it is stated that complications have not been encountered.

ROSENBAUM

Sainsbury, H.: The Estimation of Blood Pressure in Childhood with Special Reference to the Choice of Standard Cuffs. Arch. Dis. Childhood **28:** 268 (Aug.), 1953.

An attempt has been made to ascertain the extent to which the standard sizes of inflatable cuffs normally available are applicable to children of different ages, presuming that to obtain comparable readings they should enclose two-thirds of the upper arm of the children for whom they are intended.

Mean values for the size of children's arms at different ages are presented, and it was found that

the 10 cm. cuff can be used for all children between 4 and 12 years. Below 4 years only the 5 cm. cuff will fit, but children over 12 years can take the adult cuff.

In those age ranges in which these cuffs departed materially from the requirement of enclosing two-thirds of the upper arm, readings taken with the standard cuff and with a cuff folded to comply with this requirement were compared. The discrepancies, while they varied in individual cases from 0 to 20 mm. Hg, were generally small.

BERNSTEIN

Von Wallerstern, L.: Dynamics of Circulation in Pulsus Alternans. Ztschr. Kreislaufforsch. **42:** 683 (Fasc. 17/18), 1953.

In a case of pulsus alternans the various components of the mechanical cardiac cycle were calculated from simultaneous recordings of the carotid pulse curve, the electrocardiogram and the phonocardiogram. The stronger beats were characterized by shortening of the time of isometric contraction and a longer ejection time, while in the weaker beats these values changed in an opposite way. The total time of mechanical systole was longer in the larger beats. Occasional premature ventricular contractions transiently accentuated a pre-existent pulsus alternans. The first postextrasystolic pulse increases in size regardless of whether the premature beat follows a weaker or a stronger contraction.

The author explains these alterations of dynamics in the course of alternating strength of pulse waves by a variety of factors such as alternation of diastolic rest blood volume, variations of initial aortic pressure at the time of onset of ejection, and variations in recovery and conductivity of the myocardium with alternate beats.

PICK

Scheinberg, T., Blackburn, I., Saslaw, M., Rich, M., and Baum, G.: Cerebral Circulation and Metabolism in Pulmonary Emphysema and Fibrosis with Observations on the Effects of Mild Exercise. J. Clin. Invest. **32:** 720 (Aug.), 1953.

Studies in cerebral metabolism were made in 22 patients with chronic pulmonary disease of moderate severity. These were compared with normal controls of the same age, and the effects of mild exercise were studied in some of the patients. In this particular group the mean values for cerebral blood flow, AV oxygen difference, oxygen consumption, and vascular resistance did not differ significantly from the normal controls. No correlation was found between the cerebral blood flow and the arterial pressure of oxygen, or the per cent arterial oxygen saturation. However, a good correlation between the blood flow and the arterial carbon dioxide pressure was found. There was no significant effect on metabolic functions following exercise.

The authors feel that these data demonstrate the relative unimportance of the clinical and spirometric severity classification to the cerebral blood flow in chronic pulmonary disease while re-emphasizing the important relationship between the arterial carbon dioxide pressure and the cerebral blood flow.

WAIFE

PATHOLOGY

Freer, J. L., and Matheson, W. J.: Left Auricular Enlargement in Endocardial Fibroelastosis. Arch. Dis. Childhood **28:** 284 (Aug.), 1953.

Seven fatal cases of endocardial fibroelastosis are briefly described. In all, left auricular enlargement was demonstrated radiologically and this is considered to be a useful confirmatory sign in diagnosis.

BERNSTEIN

Williams, H., O'Reilly, R. N., and Williams, A.: Fourteen Cases of Idiopathic Myocarditis in Infants and Children. Arch. Dis. Childhood **28:** 271 (Aug.), 1953.

Idiopathic myocarditis is a serious, frequently fatal malady occurring usually in the first two years of life. The pathologic lesion consists of widespread but usually patchy muscle damage with an associated inflammatory cell reaction. The common clinical illness is a rapidly developing, usually fatal cardiac failure which is manifested by severe respiratory embarrassment, cyanosis, tachycardia with low or normal temperature, an enlarged heart and liver, and electrocardiographic changes of myocardial damage.

The illness in some patients may be more insidious in onset and the heart failure not so severe. Recovery frequently occurs after a long illness, but there is permanent myocardial damage. The acute form of the disorder is commonly mistaken for pneumonia, since respiratory embarrassment and cyanosis are the outstanding clinical features and cardiac enlargement is difficult and frequently impossible to detect clinically. Treatment with digitalis and oxygen has been of very definite value in some patients.

BERNSTEIN

Drennan, J. M.: Acute Isolated Myocarditis in Newborn Infants. Arch. Dis. Childhood **28:** 288 (Aug.), 1953.

Two fatal cases of acute isolated myocarditis occurring in newborn infants are described. The lesions in the myocardium were focal in distribution and showed a peculiar degenerative change limited to the sarcoplasm of the affected muscle fibres. The relationship of this parenchymatous lesion to the more common interstitial type is discussed. There was no response to treatment with various antibiotic agents.

BERNSTEIN

PHARMACOLOGY

Leeds, S. E.: Cardiac Resuscitation. J.A.M.A. 152: 1409 (Aug. 8), 1953.

There appears to be an increase in the number of patients who require resuscitation. The subject should be given thought because the delay of only a few minutes in beginning treatment may make the difference between a dead or disabled patient and a living and well one. Technics of cardiac resuscitation are discussed. The construction of defibrillator equipment is gone into carefully, and the author lists the necessities for the construction of a resuscitation kit and its adjuncts. He gives an outlined form pointing out all the instruments and drugs necessary or useful in cardiac resuscitation. It is felt that such a resuscitation kit and adjunct equipment should be available for instant use in operating rooms and wherever necessary on each ward or area in the hospital where it might be needed. At any rate, it would be wise to keep the complete kit and adjunct equipment in readiness at some central point in every hospital. One might have to depend on mouth to mouth breathing to maintain respiration until the equipment can be brought to the patient.

KITCHELL

Pollock, B. E., and Pruitt, F. W.: Oral Therapy with Mercumatilin (Cumertilin), A New Mercurial Diuretic. Am. J. M. Sc. **226:** 172 (Aug.), 1953.

In a clinical study using ambulatory cardiac patients with congestive heart failure, the authors observed the effects of treatment of fluid retention with an oral mercurial diuretic, Mercumatilin (Cumertilin). Each tablet contains the equivalent of 20 mg. of mercury and the dosage employed ranged from 1 to 5 tablets daily. No significant toxicity was recorded except looseness of the bowels which disappeared without stopping the drug. In 15 of 20 patients with heart failure resistant to digitalis and salt-free diet, addition of the oral mercurial maintained compensation. Supplements of parenteral mercurials were required in the other five patients. This oral preparation appears to be a safe and effective agent in the treatment of congestive heart failure.

SHUMAN

Kaplan, B. M., Zitman, I. H., Solarz, S. D., Miller, G., Mehlman, J. S., and Kaplan, I. G.: Clinical Experience with a New Oral Mercurial Diuretic, 3-Chloromercuri-2-Methoxypropylurea (1347). J. Lab. & Clin. Med. **42:** 269 (Aug.), 1953.

The purpose of this study was to investigate clinically a new oral mercurial diuretic, 3-chloromercuri-2-methoxypropylurea (1347 EX) (Neohydrin).

The response of each patient to the oral mercurial was classified as "good" if the parenteral mercurial was completely replaced or required infrequently. Ten of the 15 patients were classified in this group. A "fair" response consisted of partial replacement of the oral preparation or an uncertain "good" response. Five patients fell into this category. In none of the patients included in this study was there a "poor" result, and that consisted of total ineffectiveness of the drug.

The dosage of Neohydrin was found to average three tablets daily for replacement during the first week or two of therapy and one to three tablets daily for maintenance. All the tablets were usually taken with meals, but there were no complaints of intolerance if ingested on an empty stomach.

Untoward effects including stomatitis, severe diarrhea, cramps or vomiting were not encountered in any of the 15 patients in this study. In two other patients not reported in this study, cramps and diarrhea did occur. All patients were cautioned to exercise good hygiene.

Albuminuria was noted in 5 of 10 patients tested, and a slightly elevated serum urea nitrogen was observed in 3 of 9 patients examined. Neither the albuminuria nor azotemia could be attributed to the oral mercurial. In the nine patients on whom electrocardiographic and hematologic examinations were performed there were no changes that could be ascribed to the Neohydrin.

MINTZ

Pisanty, J., and Nava, A.: Digitalis-like Effects of Orange of Acridine. Arch. Inst. cardiol. Mexico. **23:** 516, (Aug. 31), 1953.

Orange of acridine caused a progressive decrease of systolic contractions and finally a systolic arrest in the isolated frog heart. When studied in heart-lung preparations of dogs or cats, this drug decreased the volume of a previously dilated heart. Doses of 15 to 50 mg. per kilogram were followed by electrocardiographic changes similar to those of digitalis. Doses of 70 mg. in the heart-lung preparation were able to overcome spontaneous heart failure, not that caused by barbiturates.

It should be noted that orange of acridine has a chemical structure quite different from that of digitalis glycosides. Its cardiac action is independent of any vagal effect.

LUISADA

Needleman, H. L., and Horwitz, O.: A Comparative Study of the Effects of Three Vasodilator Drugs, Pentamethonium Bromide (C5), Dilatol (SKF-1700-A) and Peniomide (BA-9295) on the Digital Cutaneous Blood Flow. Am. J. M. Sc. **226:** 164 (Aug.), 1953.

Control subjects and patients with peripheral vascular disease received intravenous injections of vasodilator drugs under controlled environmental conditions with measurements being made of digital cutaneous blood flow, cardiac output, pulse rate and blood pressure in a search for an agent

which would produce selective vasodilatation of the digital skin. Of the three drugs tested, Peniomide (BA-9295) caused significant increases in the digital blood flow in the majority of subjects without evidence of having produced vasodilatation elsewhere. Its action was not accompanied by a hypotensive effect or a change in cardiac output such as occurred with pentamethonium (C5). BA-9295 may be a useful drug in the treatment of peripheral arterial disease.

SHUMAN

PHYSICAL SIGNS

Bean, W. B.: Precordial Noises Heard at a Distance from the Chest. J.A.M.A. **152:** 1293 (Aug. 1), 1953.

A variety of clinical conditions which may be associated with precordial sounds heard by the unaided ear at a distance from the chest is assembled, compared, and assessed. The commonest causes of such sounds are cardiac murmurs produced by valve rupture or other lesion, interstitial mediastinal and pulmonary emphysema, spontaneous and traumatic pneumothorax, pneumopericardium, and a small mysterious miscellany of unexplained sounds. The noises considered have diverse sources and there is no physiological common denominator. With such differences in cause, in treatment, and in prognosis, the attention should be directed to the cause which usually comes to light on careful clinical scrutiny.

KITCHELL

PHYSIOLOGY

Grette, K.: Micromethod for the Determination of Calcium and Magnesium in Serum. Titration with Ethylene-diamine-tetracetate Scandinav. J. Lab. & Clin. Investigation **5:** 151 (no. 2), 1953.

A micromethod is described whereby the calcium and magnesium in 0.05 ml. of serum is determined by titration with ethylene-diamine-tetracetate with the dye Eriochrome Black T as the indicator. The sum of calcium and magnesium in the serum is determined by direct titration. Calcium is then determined after precipitation as oxalate. The oxalate is decomposed with perchloric acid making the calcium directly titratable. The difference between the two titrations represents the magnesium. The method is said to show an accuracy for calcium of 1 per cent and for magnesium of 5 per cent.

ROSENBAUM

Gifford, R. W., Estes, J. E., Code, C. F., Baldes, E. J., and Roth, G. M.: Study of Movements of Cutaneous Interstitial Fluids in Human Beings by Means of a Fluorescent Tracer Substance. J. Lab. & Clin. Med. **42:** 299 (Aug.), 1953.

The present study is concerned with the photofluorometric determination of the rate of disappearance of a fluorescent tracer (Riboflavin) after its intradermal injection. This method enables one to study the flow of interstitial fluid in human beings.

The disappearance of riboflavin after its injection in the skin of the legs of 20 normal persons was studied under basal conditions. These results were compared with those obtained after subjecting the same persons to various experimental conditions designed to alter the flow of tissue fluid.

An increase in the rate of disappearance of riboflavin, considered to indicate increased flow of tissue fluid, was observed in normal persons in a warm environment and after local injections of histamine. A slow disappearance of riboflavin, considered to indicate a slower rate of flow of tissue fluid, was observed in normal people in a cold environment, after local injections of epinephrine, and when the limb in which the injection was made was dependent or obstructed by the inflated cuff of a sphygmomanometer. No significant changes were observed in the flow of tissue fluids in the skin of the lower extremities of patients suffering from chronic occlusive arterial disease. The disappearance of riboflavin was more rapid in the skin of edematous extremities.

MINTZ

Tyrer, J. H.: The Actions of *l*-Adrenaline and *dl*-Noradrenaline on the Pulmonary Circulation of Artificially Perfused Sheep. Quart. J. Exper. Physiol. **38:** 169 (Aug.), 1953.

Both *l*-adrenaline and *dl*-noradrenaline caused a rise of mean pulmonary artery pressure in sheep artificially perfused at a constant rate thus confirming work on other species. Tachyphylaxis was encountered in the pulmonary artery pressor response to both drugs, but not in the aortic pressor responses. Synthetic *l*-adrenaline had a slightly weaker pulmonary artery pressor effect than did twice the dose of *dl*-noradrenaline.

MAXWELL

Rodbard, S.: Bronchomotor Tone. A Neglected Factor in the Regulation of the Pulmonary Circulation. Am. J. Med. **15:** 356 (Sept.), 1953.

By analyzing the factors regulating pulmonary blood flow, the author reviews the physiology of respiration and calls attention to extravascular mechanisms in the approach to the general physiology of the pulmonary circulation. His thesis is that the regulation of intra-alveolar pressure, which is in part effected by the (extravascular) bronchomotor apparatus through nervous and humoral impulses, plays a far more important role in the regulation of blood flow through the lungs than is generally appreciated. In particular, the hydrodynamic balance in the alveolar capillaries during

pulmonary edema, chronic cor pulmonale, and congestive heart failure is analyzed.

HARRIS

RHEUMATIC FEVER

Coburn, A. F., Moore, L. V., and Haninger, J.: Serum Diphenylamine Reaction in Rheumatic Fever. Arch. Int. Med. **92:** 185 (Aug.), 1953.

The substance in serum which reacts with diphenylamine to give it a purple color has not been identified. Under certain conditions its concentration increases in the blood stream. One of these conditions is a sterile inflammatory reaction, such as rheumatic fever in man and anaphylactic arthritis in the guinea pig. In the latter, when a single experimental lesion is produced the substance reaches a peak concentration in the circulation about 24 hours after the onset of inflammation. In rheumatic fever the peak appears to coincide with or follow shortly the height of rheumatic activity. The concentration of the reactive material in the blood stream, as detected by the diphenylamine reaction, appears to be conditioned by the intensity of the inflammatory process.

During this and related studies it has been observed that: (a) connective tissue is a rich source of the diphenylamine-reactive substance; (b) an inflammatory disease of the connective tissue, rheumatic fever, is accompanied by an increased concentration of this substance in the blood; and (c) increased concentration of similarly reacting material appears in the blood when the tissues around the guinea pig joint are injured by a anaphylactic reaction.

BERNSTEIN

V. Albertini, A.: The Pathogenesis of the Rheumatic Granuloma. Schweiz. med. Wchnschr. **83:** 772 (Aug.), 1953.

The author reviews the literature on the histology and pathogenesis of the Aschoff body in correlation with his own investigations. The Aschoff nodule is a form of granuloma with a specific histologic structure and is characteristic of rheumatic infection. The type of primary tissue damage which precedes the formation of the granuloma has not yet been established. Apart from fibrinoid degeneration of connective tissue, primary necrosis of muscular tissue has to be taken into consideration. The subsequent cellular reaction serves to remove the necrotic tissue. The characteristic cells are large basophilic elements, considered by the author to derive from histiocytes, which later change to the "Anitschkow cells." The latter, therefore, are not myocytes, but "cardiohistiocytes," that is interstitial cells specific for cardiac tissue, but not specific for the rheumatic process. The same type of cells may be found in the myocardium as well as in the endocardium and pericardium in a variety of pathologic conditions, such as subacute bacterial endocarditis, healing infarcts and traumatic lesions. From the viewpoint of etiology, the author's conclusions are in keeping with the opinion of others who consider acute rheumatism a streptococcic infection leading to allergic tissue reactions.

PICK

Corelli, F.: On the Prevention of Cardiac Lesions in Acute Articular Rheumatism. A New Method in the Treatment of Rheumatic Fever. Acta med. Scandinav. **143:** 450 (Fasc. 6), 1952.

The author describes a type of treatment for rheumatic fever which is said to be a complex antiexudative, desensitizing, aspecific, antiallergic, antihistaminic, capillary permeability reducing therapy. It consists of (1) aminopyrine, antihistaminic substances and calcium, (2) exclusion of any biologic or pyretogenous stimulant therapy, (3) rest in bed over a long period, and (4) continuous oxygen therapy for two to three weeks. It is stated that 50 successive patients, suffering their first attack, who were treated in this way, recovered quickly and without valvular lesions. No new cardiac lesions and no aggravation of those already present were observed in 156 cases of relapses of rheumatic fever. The importance of early diagnosis and early intense therapy is stressed.

ROSENBAUM

Oka, M.: A Nicotinic Acid Ester ("Trafuril") Skin Test in Rheumatic Diseases. Acta med. scandinav. **145:** 258 (no. 4), 1953.

The skin reaction caused by smearing a thin layer of Trafuril ointment (tetrahydrofurfuryl nicotinic acid ester) on the volar surface of the forearm was studied in various rheumatic diseases and in normal subjects. A positive result consists of the appearance of erythema and swelling, surrounded by an inflamed ring. Positive reactions occurred in nearly 95 per cent of 69 control subjects. More than two-thirds of a group of 255 patients with various forms of chronic arthritis showed negative reactions. There were no cases of rheumatic fever studied, but the author predicts that the reaction during the active period will be negative, becoming gradually positive as the subject improves. Treatment with cortisone and corticotropin tends to make the reaction stronger. More positive reactions were observed in patients with rheumatoid arthritis during reactions to gold therapy such as eosinophilia and dermatitis.

ROSENBAUM

SURGERY IN HEART AND VASCULAR SYSTEM

Moretz, W. H., and Bray, P. F.: Observations on the Effects of Carotid-jugular Anastomoses. Am. Surgeon **19:** 765 (Aug.), 1953.

Five patients with a variety of neurologic deficits

were subjected to a right carotid-jugular anastomosis for periods of from 4 to 24 months. Cerebral angiograms revealed no revascularization of the brain. No significant improvement in cerebral function was noted. Undesirable side effects were common, although usually reversible if the shunt was eradicated. The authors recommend that the procedure be abandoned.

WESSLER

Kirklin, J. W.: Surgical Treatment of Anomalous Pulmonary Venous Connection. Proc. Staff Meet., Mayo Clin. **28**: 472 (Aug.), 1953.

The anomalous vein draining the entire left lung was found to empty into the left innominate vein at the apex of the thorax. The entire venous trunk was mobilized, as was the left pulmonary artery. A clamp was placed on the left pulmonary artery to prevent congestion of the lungs while the venous outflow was obstructed. It was apparent that the left auricular appendage was of such size that its removal would leave a defect in the left atrium approximately the size of the anomalous vein. A Satinsky clamp was placed on the auricular wall below the base of the auricular appendage. The appendage was then excised, leaving an oval defect in the auricular wall. Digital exploration of the left auricle through this defect revealed only one venous orifice within the auricle; from its position, it appeared probable that this was the common orifice of the right pulmonary veins. A small auricular septal defect, about 1 cm. in diameter was noted.

After the clamp was replaced on the auricular wall, an anastomosis was made between the anomalous trunk and the left auricle. The thin-walled vein was sutured accurately to the endocardium of the auricle rather than to the full, somewhat thick auricular wall so as to assure a smooth surface across the line of attachment. When all clamps were removed, the trunk made a smooth curve over the hilus of the lung and lay in its new position without tension or kinks. Flow through the anastomosis appeared to be excellent.

SIMON

Palumbo, L. T., and Paul, R. E.: Effects of Ligation of Major Veins. Angiology **4**: 337 (Aug.), 1953.

Ligation of the inferior vena cava, common iliac or superficial femoral vein was performed in 21 male patients for a postphlebitic syndrome or an acute phlebitic process with or without pulmonary infarction.

The authors conclude that ligation of major veins to prevent recurrent episodes of pulmonary infarction is a life saving procedure and is usually not followed by enough disablement or impairment of function of the extremity to prevent the patients from returning to their previous or to an adequate means of livelihood.

Major vein ligation in the presence of an acute thromboembolic process carries with it less disability than similar procedures in patients with a postphlebitic syndrome.

WESSLER

Mendelsohn, H. J.: Prevention and Management of Injuries to the Pulmonary Vessels During Pulmonary Resection. Arch. Surg. **67**: 276 (Aug.), 1953.

The causes of injury to the pulmonary vessels during pulmonary resection are described and methods for their prevention, for the control of hemorrhage and for repair of the injured vessels are outlined. From an experience involving more than 250 pulmonary resections, 11 cases are reported in detail in which pulmonary vascular injuries were repaired.

WESSLER

Hurwitt, E. S., Bloomberg, A., Aaron, R., Jezer, A., and Young, D.: An Appraisal of the Surgical Treatment of Mitral Stenosis. Ann. Surg. **138**: 219 (Aug.), 1953.

The indications for mitral commissurotomy are described and listed as follows: "Exertional dyspnea, orthopenea, paroxysmal nocturnal dyspnea, hemoptysis, peripheral emboli, congestive failure and episodes of paroxysmal arrhythmia." These have constituted the authors' cardinal indications for operation. Likewise, the contraindications to mitral commissurotomy have been listed. They are: "Active rheumatic fever, subacute bacterial endocarditis, and significant left ventricular enlargement." Thirty-four cases are described in which finger fracture valvuloplasty was done on 28 cases with no deaths; in the group taken to the operating room six additional cases were not operated on with three deaths in this group. Preoperative preparation, anesthesia, surgical technic and postoperative results are presented. Three situations were encountered in which mitral valvular commissurotomy could not be performed for technical reasons. These are: obliteration of the auricular appendage by thrombus, massive calcification of the valve and valve ring, and a giant left auricle. It is pointed out that the role of surgery in mitral stenosis is not definitive but only palliative. This palliation may be extraordinary in degree or minimal in character. Every one of these patients has rheumatic heart disease after operation as well as before, and the role of surgery must be appraised as a component factor in the over-all, long-term management of the rheumatic cardiac.

DENNISON

VASCULAR DISEASE

Novack, P., Shenkin, H. A., Bortin, L., Goluboff, B., and Soffe, A. M.: The Effects of Carbon Dioxide Inhalation upon the Cerebral Blood

Flow and Cerebral Oxygen Consumption in Vascular Diseases. J. Clin. Invest. **32:** 696 (Aug.), 1953.

The inhalation of 5 per cent carbon dioxide results in a marked and selective cerebral vasodilatation in normal young individuals and results in an increase in cerebral blood flow. Using the nitrous oxide technic, these authors studied the effect of carbon dioxide in patients with vascular disease. Normotensive individuals were compared to elderly arteriosclerotic but normotensive individuals, hypertensive individuals without evidence of arteriosclerosis, and subjects with hypertension and arteriosclerosis.

The results indicate that the normotensive arteriosclerotic subjects fail to show a significant decrease in cerebrovascular resistance although the blood flow is increased slightly. A small group of patients with essential hypertension responded normally to carbon dioxide inhalation when hypertension and arteriosclerosis coexisted. The severity and diffuseness of the arteriosclerosis appears to be much greater, and there is an increased persistent vascular tone. The net effect is a great increase in cerebrovascular resistance with a marked reduction in cerebral blood flow and oxygen consumption.

The authors suggest that this technic may provide a convenient means of estimating and associating the components of increased cerebrovascular resistance.

WAIFE

Edwards, J. E.: Pathologic and Developmental Considerations in Anomalous Pulmonary Venous Connection. Proc. Staff Meet. Mayo Clin. **28:** 441 (Aug.), 1953.

Distinction should be made between the two types of anomalous pulmonary venous connection, namely total and partial. In total anomalous connection, both right-to-left and left-to-right shunts are present, whereas partial anomalous pulmonary venous connection is responsible for a left-to-right shunt only. Prognosis is usually poor in the total form; the majority of patients who have such an anomaly die in infancy. The prognosis in partial anomalous pulmonary venous connection is generally good; many patients who have this form of anomaly reach adult life.

The developmental basis for anomalous pulmonary venous connection into a systemic thoracic vein, into an abdominal vein or into the lower portion of the right atrium depends on retention of an embryonic connection which is normally lost, coupled with failure of the developing pulmonary veins to make the normal secondary connection with the heart. In those cases in which the anomalous pulmonary venous connection is with the upper aspect of the right atrium, the malformation may depend on abnormal positioning of the atrial septum.

SIMON

Swan, H. J. C., Burchell, H. B., and Wood, E. H.: Differential Diagnosis at Cardiac Catheterization of Anomalous Pulmonary Venous Drainage Related to Atrial Septal Defects or Abnormal Venous Connections. Proc. Staff Meet. Mayo Clin. **28:** 452 (Aug.), 1953.

Problems encountered in the diagnosis of partial anomalous pulmonary venous drainage are not solved readily by clinical methods or by the usual cardiac catheterization technics. Diagnosis of such conditions by demonstration and localization of the site of arterialization in the right atrium or its tributaries is greatly facilitated by the use of the cuvette oximeter. However, when the anomalous vein connects directly with the right atrium, differentiation from atrial septal defect is often a difficult problem, even when the catheter is manipulated successfully into the vein.

Differences in the recorded patterns of dilution of an indicator (T-1824) during its initial circulation after injection into a pulmonary vein and the venae cavae or into the left and right pulmonary arteries will demonstrate the presence or absence of functional anomalous venous drainage resulting from abnormal venous connections. However, in patients who have atrial septal defects and extremely large pulmonary flows, it often can be demonstrated that blood draining from the right lung is shunted preferentially across the defect. In such cases, a much greater degree of functional anomalous pulmonary venous drainage may occur from the right lung than from the left without the presence of an anomalous venous connection; the possibility of an anomalous vein cannot usually, however, be completely excluded.

In patients who have atrial septal defects, it is often possible by means of dilution curves recorded following injection of dye into the right atrium or the venae cavae to demonstrate right-to-left shunts of a magnitude too small to cause demonstrable desaturation of arterial blood. In a portion of such patients, dye curves recorded following injections into the venae cavae demonstrate that the proportion of blood draining from the inferior vena cava which is shunted from right to left across the defect is larger than the proportion of similarly shunted blood draining from the superior vena cava.

SIMON

Duff, F.: Greenfield, A. D. M., and Whelan, R. F.: Vasodilatation Produced by Experimental Arterial Gas Embolism in Man. Lancet **2:** 230, (Aug. 1), 1953.

During the course of an investigation of the local effects of carbon dioxide on peripheral blood vessels, small quantities of gaseous carbon dioxide were

injected into the brachial artery. Pronounced increase in blood flow through the limb was observed. Other gases were equally effective in producing this pronounced increase in flow and the same gases dissolved in saline had no appreciable effect. The mechanism, therapeutic possibilities, and theoretic implications are discussed.

McKusick

Schieve, J. F., and Wilson, W. P.: The Influence of Age, Anesthesia, and Cerebral Arteriosclerosis on Cerebral Vascular Activity to CO_2. Am. J. Med. **15**: 171 (Aug.), 1953.

Cerebral vascular reactivity to carbon dioxide is high in normal adult people of all age groups, and there is only gradual reduction in reactivity with the normal aging process. In severe cerebral vascular disease, cerebral vascular reactivity to carbon dioxide is greatly reduced. The response to carbon dioxide is altered by thiopental anesthesia deep enough to reduce the cerebral metabolic flow by 40 per cent. Cerebral vascular reactivity to carbon dioxide can be utilized to separate certain patients with senile dementia due to primary parenchymal brain damage from those with dementia secondary to cerebral vascular disease. A normal high increase in cerebral blood flow after carbon dioxide makes the diagnosis of generalized cerebral vascular disease highly improbable while a poor response may or may not indicate its presence.

Harris

Edholm, O. G., and Howarth, S.: Studies on the Peripheral Circulation in Osteitis Deformans. Clin. Sc. **12**: 277 (Aug.), 1953.

Studies were made in 18 cases of active osteitis deformans. Peripheral blood flow was measured in 21 out of 23 affected limbs, using a venous occlusion plethysmograph. Estimations of bone blood flow were also made in four cases. In all of the foregoing, evidence of increased blood flow was found. It was also noted that skin temperatures were increased in areas overlying actively diseased bones, and that these temperatures did not fall on exposure. On the other hand, areas on affected limbs not overlying the diseased bones showed normal skin temperatures which did fall on exposure. Intravenous injection of epinephrine resulted in a fall in blood flow in two affected limbs, indicating constriction of bone blood vessels. An increase in bone vascularity in the active phase of the disease was demonstrated by bone biopsy and by autopsy studies. These indicated that the increased flow through bone was chiefly by way of an increase in periosteal plexus flow and to a lesser extent by increased flow through the nutrient artery.

Enselberg

Jackson, A., and Slavin, M.: Dissecting Aneurysm of the Aorta. Report of Six Cases with Etiopathologic and Diagnostic Considerations. Angiology **4**: 357 (Aug.), 1953.

Six cases of dissecting aneurysm are reported and variations in the clinical picture are discussed. The aneurysm is caused by bleeding from the vasa vasorum into a weakened and degenerated media. Weakening of the media may be causally related to congenital malformations, chemical or hormonal disturbances and atherosclerosis. When dissection starts with an intimal tear, hypertension is an important contributing factor.

Wessler

Jahnke, E. J., Jr., and Seeley, S. F.: Acute Vascular Injuries in the Korean War: an Analysis of 77 Consecutive Cases. Ann. Surg. **138**: 158 (Aug.), 1953.

The authors reported on the treatment of 77 consecutive vascular injuries sustained in the Korean war. The lesions were divided into those affecting either minor or major arteries. Thirty-two occurred in the upper extremity and the remainder in the lower.

With regard to therapy, lesions of minor arteries were ligated unless it was obvious that such a procedure would result in arterial insufficiency and gangrene. All major vascular injuries were repaired without regard to the size of the defect and the length of time between wounding and operation. The procedure consisted either of transverse suture anastomosis, end-to-end suture anastomosis or the use of vein grafts.

Of the 43 minor vascular injuries treated, gangrene, requiring amputation, occurred in five patients. In the case of the 34 major vascular injuries, only three extremities were amputated. Because of the good results obtained in the latter group, it was recommended that in every instance attempts should be made to repair an acute major arterial injury.

Abramson

Winsor, T., and Selle, W. A.: The Effect of Venous Compression on the Circulation of the Extremities. Arch. Phys. Med. & Rehabilitation. **34**: 559 (Sept.), 1953.

These studies are in accord with those of others who were unable to demonstrate an increase in blood flow after intermittent venous occlusion. Venous occlusion for five minutes with a pressure of 40 mm. of mercury in normal and arteriosclerotic subjects resulted often in a decrease in blood flow.

Directional limb compression using 13 cuffs was not effective in increasing the skin temperature, the pulse volume or the blood flow of the toe, regardless of the direction of compression, even though these patients showed considerable vasodilation following alcohol and heat. In two patients lymphedema was decreased. Such changes were observed after 30 minutes of treatment with the direction of compression upward. This beneficial action on lymphedema may have occurred locally by means of the increased external pressure on the tissues and the stripping of the lymphatic vessels of their contents without

producing general changes in lymph circulation. Further studies are indicated.

BERNSTEIN

Hines, L. E., Catlin, J., and Kessler, D. L.: Tests for So-called Capillary Fragility of the Skin and the Significance of Positive Tests in Vascular Disease. Am. J. Med. **15**: 175 (Aug.), 1953.

Using a negative suction test to determine capillary fragility, the authors found a higher incidence of positive tests in older patients. Patients with diabetes mellitus and hypertension or other vascular diseases showed an extremely high incidence of positive capillary fragility tests. All patients with hypertension as well as those with arteriosclerotic disease without hypertension showed a moderately high incidence of positive fragility tests.

HARRIS

Semple, R.: Diabetes and Peripheral Arterial Disease. Lancet **264**: 1064 (May 30), 1953.

The author attempted to determine whether there was any difference between arterial disease occurring in diabetics and in nondiabetics. The study was carried out in 100 unselected diabetics and in 52 cases of gangrene. On the basis of the analysis of his results the author arrived at certain conclusions.

First, the severity of the diabetes bore little relation to the occurrence of arterial disease. Secondly, arteriosclerotic disease of the legs in diabetics was associated with the early appearance of gangrene, while in nondiabetics, intermittent claudication commonly preceded such an event. From such findings it was concluded that in diabetics with arterial impairment, the femoral and popliteal arteries were relatively unaffected, while the brunt of the lesion fell on the more distal vessels.

ABRAMSON

Gryspeerdt, G. L.: Venography of the Lower Limb. Brit. J. Radiol. **26**: 329 (July), 1953.

The author describes a modification of the technic used in the venographic study of the valves in the deep venous system. This consists of the addition of the Valsalva maneuver to the method of ascending venography. A small cut-down is made over a suitable vein on the dorsum of the foot and a polythene catheter is passed up the vessel for 1 cm. The catheter is connected with a simple positive-pressure saline infusion apparatus, controlled by a sphygmomanometer. A rubber tube is applied around the lower portion of the leg, in order to occlude the superficial venous system, and 50 cc. of 35 per cent Diodone are injected through the catheter. With 10 cc. of the radio-opaque material still in the syringe, the patient performs the Valsalva maneuver which consists of closing his lips, holding his nose and expiring forcibly. This step tends to force the material backward and in so doing it visualizes the normal valves. If the latter are incompetent, they will not be demonstrated by such a measure. By use of Valsalva blowing by the patient, the contrast medium can be retained in the region being examined so as to permit the veins to be studied individually. Through this technic, incompetent communicating veins can also be readily identified.

ABRAMSON

MacKenzie, D. A., and Clogett, O. T.: Unusual Aneurysm of a Pulmonary Artery. J. Thoracic Surg. **25**: 524 (May), 1953.

A case report is presented of an aneurysm of a pulmonary artery which was successfully treated surgically. Initial examination revealed a loud systolic murmur heard over both sides of the upper and anterior part of the thorax, being slightly more intense on the left side. At times it was continuous, particularly at the end of deep inspiration. Roentgenograms demonstrated a vascular anomaly in the upper lobe of the left lung which was considered to be a large vessel. Oximetric studies appeared to exclude pulmonary arteriovenous fistula.

When surgical exploration was carried out, a large pulsating mass was found. In order to remove it, the upper lobe of the left lung was excised. The patient made an uneventful recovery. Examination of the specimen revealed fusiform dilatation of the pulmonary artery to the upper lobe. Injection of the vascular tree did not demonstrate any evidence of an arteriovenous fistula.

ABRAMSON

Wilson, M. G.: A Method of Treatment for Varicose Veins. Lancet **264**: 1273 (June 27), 1953.

After reviewing the various methods utilized in the treatment of varicosities, the author described a relatively new procedure. Using a nonabsorbable suture material, he passed subcutaneous ligatures around incompetent veins at various levels. In each instance, two nicks were made in the skin, one on each side of the vessel. A large circle needle, threaded with braided nylon, was passed, blunt end first, through one nick, then under the vein and out the other, leaving the ligature in its track. It was reinstated, blunt end first, through the second nick and passed under the skin but over the vein, to emerge through its original point of entry. The two ends of the ligatures were then pulled backward and forward once or twice, to enable the suture material to slip through the fat around the vein, and tied tightly with three hitches. When the free ends were cut off and the skin straightened, the knots disappeared under the skin.

Coupled with high ligation, multiple ligature was found to give better end results than the other commonly used procedures. However, it was necessary to use many ligatures in order to accomplish the desired aim. The procedure was not complicated by the delayed healing and minor sepsis which may follow multiple incision in the leg. Furthermore, no

visible scar was produced. Another advantage was that the method was much shorter than the use of incisions.

ABRAMSON

Cockett, F. B.: The Practical Uses of Venography. Brit. J. Radiol. **26**: 339 (July), 1953.

Attention is called to the use of venography in elucidating the problem of ulceration associated with the postphlebitic syndrome. With the aid of the Valsalva modification, this procedure is of value in demonstrating the presence of incompetent deep venous channels following acute deep thrombophlebitis. It is also important in outlining incompetent communicating veins which may in great part be responsible for the existence of ulceration by maintaining a state of venous stasis in the involved region. As a result of such information, proper surgical therapy can be instituted to rectify the unphysiologic state and hence contribute to permanent healing of the nutritional disturbance.

ABRAMSON

Geraci, J. E., and Kirklin, J. W.: Transplantation of Left Anomalous Pulmonary Vein To Left Atrium. Proc. Staff Meet., Mayo Clin. **28**: 472 (Aug.), 1953.

The patient who is the subject of this report was considered on preoperative examination to have an anomalous left pulmonary vein draining the blood of the entire left lung and emptying into the left innominate vein. This anomalous vein was transplanted successfully into the left atrium. The patient's convalescence was marred only by transient bronchopneumonia that appeared two weeks after operation. Postoperative cardiac catheterization revealed normal blood-oxygen saturation values in the superior vena cava and right atrium. The systemic cardiac output at this time was 9.0 liters per minute and the pulmonary flow was 10.4 liters per minute. This difference perhaps is indicative of a small left-to-right flow through the atrial septal defect.

When the patient was dismissed, the cardiac auscultatory findings were normal and no murmurs were heard. Thoracic roentgenograms, taken three weeks and five months after operation, showed some diminution in the size of the heart and the mediastinal vascular shadow. A follow-up examination five months after dismissal, revealed that the patient's fatigability and dyspnea on effort had disappeared and that he felt normal. His tolerance to exercise had improved considerably.

SIMON

Mankin, H. T., and Burchell, H. B.: Clinical Considerations in Partial Anomalous Pulmonary Venous Connection. Proc. Staff Meet., Mayo Clinic. **28**: 463 (Aug.), 1953.

The serious consequences of this vascular anomaly are not caused by abnormal pulmonary function, but rest largely on the increased burden to the right side of the heart. When pulmonary recirculation occurs, the right ventricle must maintain a pulmonary arterial flow equal to the systemic output plus the volume of blood that is recirculated.

A clinical study has been made in two cases of partial anomalous pulmonary venous connection in association with other unusual defects. The findings in one case were typical of anomalous pulmonary venous connection with anomalous drainage. In the second case, an anomalous connection was present; however, since the blood from the anomalous vein ultimately emptied predominantly into the left atrium, actual anomalous drainage was not present. The value of cardiac catheterization and the arterial dye-dilution technic after injection of T-1824 into various cardiovascular sites for the elucidation of these diagnostic problems is emphasized.

SIMON

McCune, W. S., Samadi, A., and Blades, B.: Experimental Aneurysms. Ann. Surg. **138**: 216 (Aug.), 1953.

With improved surgical methods for the direct treatment of arterial aneurysms—by excision, grafting, bypassing and wrapping—the need has arisen for more extensive study of these problems in the experimental laboratory. This work has been hampered, however, by the lack of a satisfactory method for the production of aneurysms in experimental animals. In performing necropsies upon patients who have been treated by intra-arterial nitrogen mustard for advanced malignancy, it was observed that small aneurysms are sometimes found at the site of injection of the mustard. Following this suggestion, solutions of nitrogen mustard of varying strengths were injected in the walls of dogs' aortas. It was found that destruction of the media resulted in aneurysmal dilatation of the vessel wall, leading to rupture of the aorta within 4 to 28 days, depending upon the concentration of the necrotizing agent. This method of aneurysm formation has several advantages. The lesions are produced easily within a short period of time. They form with constancy and rupture consistently so that an end point is provided for experimental procedures aimed at their prevention or treatment. The principal disadvantage of the method has been the fact that the degree of dilatation in most instances is not great, since rupture occurs early.

DENNISON

Edward, E. A.: The Anatomic Basis for Ischemia Localized to Certain Muscles of the Lower Limb. Surg., Gynec. & Obst. **97**: 87 (July), 1953.

On the basis of anatomic studies in cadavers, the author reached some conclusions regarding the arterial blood supply of the muscles in the lower extremities. He found that certain characteristics of this portion of the vascular tree were responsible for the vulnerability of local muscle groups to ischemia. First, the circulation to a muscle was found to

be an isolated unit, the nutrient artery having no substantial connection with vessels of neighboring structures. Secondly, when the muscle arteries were multiple, they frequently entered at one localized site, where injury could readily involve all of them. Furthermore, no anastomoses were present external to the muscle between a number of arteries supplying it. The lack of significant collaterals for the muscle arteries was considered to be one of the factors responsible for the frequent absence of amelioration of claudication after sympathectomy.

ABRAMSON

Gardner, F., and Oram, S.: Persistent Left Superior Vena Cava Draining the Pulmonary Veins. Brit. Heart J. **15**: 305 (July), 1953.

The clinical picture of persistent left superior vena cava draining the pulmonary veins is described and illustrated by four individuals—an infant, and persons aged 24, 24, and 13 years respectively. The general development of the patient may not be affected. Dyspnea may be the only important symptom. Physical examination shows a right ventricular cardiac impulse, accentuation of the pulmonary second sound with expansile pulsation and a diastolic shock palpable over the pulmonary artery. A systolic murmur is present to the left of the sternum and, at times, so too is a diastolic. A mitral systolic murmur may also be heard. The electrocardiogram shows right bundle branch block. X-ray shows a large ovoid shadow in the superior mediastinum enveloping the aorta and pulmonary artery. Angiocardiography may demonstrate the abnormal course of circulation and catheterization, and the highly oxygenated blood in the left innominate vein and right superior vena cava. Prognosis depends upon the amount of blood diverted to the right atrium.

The only radical treatment is anastomosis of the left superior vena cava or of the innominate vein to the left atrium or its appendage.

SOLOFF

Friedell, M. T.: Effect of Cigarette Smoke on the Peripheral Vascular System. J.A.M.A. **152**: 897 (July 4), 1953.

The author studied the peripheral vascular system by means of injected radio-active iodinated albumin and a scintillation counter. The changes in the scintillation count in the extremities of an individual after the smoking of cigarettes was used as a direct indicator of volumetric change in the extremity. The author reaches the conclusion that men and women are not equally sensitive to tobacco smoke, and approximately one out of every five persons does not receive sufficient nicotine to effect the peripheral circulation in the standard test period (the smoking of one cigarette over a period of four minutes). It was felt that some persons tested did not inhale and that possibly it is the method of smoking rather than the effect of smoking that causes a lack of change in some individuals. Vasoalterative effect of smoking could be reduced by the addition of an efficient filter. The desirability of using such filtration seems to be indicated more in women than in men because of the special sensitivity of their peripheral vascular systems. It was also noted that many older persons did not show change, which would indicate that either these persons do not inhale when they smoke or they have less sensitive peripheral vascular systems. The principle of filtration of tobacco smoke is probably a good one and the author feels it should be used by both men and women.

KITCHELL

Haxton, H. A.: Paravertebral Block with Aqueous Phenol in the Treatment of Vascular Disease. Angiology **4**: 268 (June), 1953.

The author reports on the use of 6 or 10 per cent aqueous phenol for sympathetic block in 400 cases of circulatory disorders in the extremities. Lasting effects are achieved because the phenol produces a destruction of the ganglion cells. The technic of lumbar and thoracic injections are described in detail. Although the method is not as reliable as open operation in securing sympathetic denervation, a very complete sympathetic interruption is obtained in two-thirds of the cases. Injection of phenol is indicated particularly in patients in whom the local lesion would benefit from a sympathectomy but in whom a poor general condition precludes surgery. Injections of phenol have been of benefit in arteriosclerotic ischemia of the foot, intermittent claudication, erythrocyanosis, Raynaud's disease, acute thrombophlebitis, postphlebitic syndrome and hyperidrosis. About 10 per cent of patients develop hyperesthesia in the groin after lumbar injection from irritation of the genito-femoral nerve. About 20 per cent of patients develop intercostal neuritis after cervicothoracic injection though the neuritis is usually mild and of less than two months' duration.

WESSLER

OTHER SUBJECTS

Baird, E. E., and Stembridge, V. A.: Fluid and Electrolyte Imbalance; Limitations of Plasma Sodium Levels as a Measurement of Dehydration. Texas J. Med. **48**: 576 (Aug.), 1952.

Dehydration is a common finding in two otherwise distinctly different syndromes. The water depletion syndrome is recognized from its signs of thirst and oliguria. The dehydration incident to salt depletion is not readily recognized because of the absence of signs and symptoms commonly accepted as being typical of dehydration. The mixed type of dehydration evokes the signs and symptoms of a water depletion syndrome and not those of a low salt syndrome.

Sodium concentration of the blood is an exceedingly poor indicator of the severity or even the presence of dehydration. Urine volume together with

its salt can be utilized to exclude dehydrated states as well as to indicate the possibility of their presence.

BERNSTEIN

Bing, R. J., Siegel, A., Vitale, A., Balboni, F., Sparks, E., Taeschler, M., Klapper, M., and Edwards, S.: Metabolic Studies on the Human Heart in Vivo. 1. Studies on Carbohydrate Metabolism of the Human Heart. Am. J. Med. **15**: 281 (Sept.), 1953.

After measuring the myocardial extraction and usage of glucose, lactate and pyruvate in 53 patients with and without cardiac failure and then estimating the relative contribution of their catabolism to the oxidative metabolism of the heart (the oxygen extraction ratio) and the conversion of oxidative energy from these carbohydrates into cardiac work (the energy conversion factor), the investigators found that the total aerobic metabolism of these carbohydrates fell short of the total oxygen consumption of the heart. These data indicates that the heart, for provision of energy, uses either heart muscle glycogen or noncarbohydrate substances, the latter being more likely. Spontaneous rises in arterial glucose and lactate concentration were followed by an increase in their myocardial extraction and usage. At glucose blood concentrations above 110 mg. per cent no further uptake of glucose by the myocardium was noticeable. When the arterial blood glucose concentration was suddenly raised, as the result of infusion, an upper limit of glucose extraction appeared to be absent. This might have resulted from glycogenesis as well as increased oxidation of glucose. Pyruvate was utilized by the human heart.

In low and high output failure, myocardial glucose and lactate extractions and the glucose and lactate oxygen extraction ratios were elevated; the glucose and lactate energy conversion factors were lowered. This indicates that the hyper- and hypokinetic heart in failure has become deficient in converting the energy derived from the aerobic breakdown of glucose and lactate into mechanical work.

HARRIS

Marks, P. A., and Roof, B. S.: Pericardial Effusion Associated with Myxedema. Ann. Int. Med. **39**: 230 (Aug.), 1953.

Two cases of long standing and massive pericardial effusion, proved by pericardial paracentesis, and belatedly recognized to be due to myxedema are described. Three years prior to admission to the hospital the patient had been given a six weeks' course of streptomycin therapy on the presumption that she might have had tuberculous pericarditis. For two years prior to admission the patient had noted some mental slowness and memory defect. Dryness of the skin had been present for three or four years. Physical examination revealed findings consistent with pericardial effusion; no murmurs were heard; the liver was slightly enlarged; there was no ascites; moderate bilateral pitting pretibial edema was present. The roentgenogram of the chest revealed an enlarged cardiac shadow consistent with pericardial effusion. The cardiac pulsations were diminished in the fluoroscope. The T waves were of low voltage in most of the leads. The basal metabolic rate was minus 48 per cent. Radioactive iodine uptake was 7 per cent over the thyroid gland after 24 hours. The serum cholesterol was only 271 mg. per 100 cc. After the relationship of myxedema to the pericardial effusion was recognized, therapy with thyroid extract was instituted, following which the patient made a progressive recovery. The second case was that of a 54 year old Negro female who had developed progressive weight gain, increased sensitivity to cold and progressive dyspnea on effort. Her basal metabolic rate was minus 28 per cent and x-ray of the chest revealed enlargement of the cardiac shadows suggestive of pericardial effusion. An elevated arterial blood pressure was also observed. Mercuhydrin injections for increasing dyspnea failed to effect a diuresis. The serum cholesterol was 290 mg. per 100 cc. with 70 per cent esters. Radioactive iodine uptake with 40 microcuries of radioactive iodine was 3 per cent uptake over the thyroid region in 24 hours. Protein bound iodine was 1.2 gamma per cent, the normal being 3.5 to 7.5. Thyroid therapy was instituted, following which the patient became brighter and more active and her weight fell 15 pounds. A chest film taken eight weeks after thyroxin therapy was begun showed a reduction of 3.2 cm. in the transverse diameter of the heart. Subsequently thyroid extract was substituted and eventually all evidences of congestive failure disappeared and the cardiac shadow became normal in size. Prior to treatment with thyroid extract a pericardial paracentesis had been performed; 250 cc. of straw-colored fluid had been removed, thus substantiating the diagnosis of pericardial effusion.

WENDKOS

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.

Telephone GRamercy 7-9170

AMERICAN HEART ASSOCIATION PROGRAM AT AMA MEETING

The American Heart Association will be represented by a special program at the 103rd Annual Meeting of the American Medical Association, to be held at the Civic Auditorium in San Francisco from June 21-25. The program will consist of a four-day "Question and Answer" Conference on various aspects of cardiovascular disease similar to the series conducted by the Association at the AMA Annual Meeting in Chicago in June, 1952. The program has been arranged by Howard B. Lewis, M.D., University of Oregon School of Medicine. An exhibit of professional educational materials available from the Association is also planned.

COUNCIL ON RHEUMATIC FEVER AND CONGENITAL HEART DISEASE

A special program devoted to a discussion of rheumatic fever will be presented at the Annual Meeting of the American Rheumatism Association at the St. Francis Hotel, in San Francisco, on Saturday morning, June 19. The program will be presented in conjunction with the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association. The program is as follows:

1. Natural History of Hemolytic Streptococcal Infection in Children. Lowell A. Rantz, San Francisco
2. Functional Status of the Pituitary Adrenal System in Rheumatic Fever. Vincent C. Kelley, Salt Lake City
3. Prophylaxis Against Group A Streptococci in Rheumatic Fever Patients by the Use of Single Monthly Injections of N,N′ dibenzylethylenedyamine dipenicillin G. Gene H. Stollerman, Jerome H. Rusoff and Ilse Hirschfeld, Irvington-on-Hudson, N. Y.
4. Rheumatic Heart Disease in Colorado School Children. H. J. Dodge, J. A. Lichty, Denver

SECOND WORLD CONGRESS OF CARDIOLOGY AND 27TH SCIENTIFIC SESSIONS OF THE AMERICAN HEART ASSOCIATION

All those planning to attend the Congress, scheduled to convene in Washington, D. C., September 12 through 17, are urged to *submit their applications at the earliest possible date to facilitate arrangements for groups participating in the scientific tours and social functions.* Because these groups will be limited in number, those who register for the Congress will receive a special Form C, on which they may indicate their choice of the medical sightseeing tours of scientific significance, in addition to the social functions, such as the banquet and receptions. *Any physician who is interested may attend the Congress by filling out and sending in the application blank and paying the required registration fee.* Detailed information concerning the Congress is available from the Secretary-General, L. W. Gorham, M.D., Second World Congress of Cardiology, c/o American Heart Association at 44 East 23rd Street, New York 10, N.Y.

Medical Tours

A highlight of the Congress program will be a series of medical sightseeing tours to institutions of scientific interest. On Wednesday, September 15, from 2:30 to 5:30 p.m., participants may attend lectures, demonstrations and exhibits dealing with various aspects of cardiology which are planned as follows:

Auditorium of Armory—Clinical Pathologic Conference.

George Washington University Hospital
Cardiovascular teaching technics. Clinical aspects of angiocardiography. Ballistocardiography.

Georgetown University Medical Center
Color moving picture, "Use of Artificial Kidney." Demonstrations in Renal Research Laboratory. Surgical treatment of aortic insufficiency.

Howard University Medical School
Angiocardiographic and cardiac catheterization studies. Embryonic cardiovascular anomalies. Experimental hypertension in animals. Potassium accumulation and heart function during nonspecific stresses. Technic of instruction of heart beat set to music.

Children's Hospital
Endocardial fibroelastosis, case demonstrations and autopsy findings. Hypothermia and cardiotomy in the treatment of congenital heart disease.

Veterans Administration Hospital, Mt. Alto
Anesthesiometer demonstration. Diffusion of gas through lungs of cardiac patients and normal persons. Evaluation of patients with mitral stenosis and commissurotomy. Adrenalectomy for hypertension. Exhibit of myocardial infarction and its common complications.

National Naval Medical Center
Radioactive isotopes in diagnosis and therapy. Tissue transplantation. Case reports from cardiologic department. Surgical concepts and technics of tissue transplantation.

Walter Reed Army Medical Center
Auditory and visual aids in group teaching. Cardiac catheterizations and angiocardiographic findings in 200 patients.

Army Medical Service Graduate School
Surgical repair of vascular injuries.

Research Laboratories of Army Medical Service Graduate School
Demonstration and discussion of pressure flow in pulmonary bed of lung before and after pulmonary embolism. Demonstration of method; hypothermia; dye dilution; cardiac biopsy; strain gauges; optical manometers; spectrophotometric technics; meter measurement of gas composition and paper electrophoretic technics.

Armed Forces Institute of Pathology—Conducted tours

U. S. Public Health Service, National Heart Institute—Conducted tours
Discussion of programs, grants, research, fellowships, traineeships by Director, James Watt, M.D.

A sightseeing program on Friday afternoon, September 17, will include conducted tours of the Armed Forces Institute of Pathology and its Medical Museum; Armed Forces Medical Library; and the National Heart Institute. Dr. Watt's discussion at the National Heart Institute will be repeated.

Membership

A registration fee of $25.00 has been established for the combined World Congress and Scientific Sessions. Although it has been customary in previous years to waive registration fees for professional members of the American Heart Association attending the Annual Scientific Sessions, the heavy expense entailed by the enlarged and integrated sessions of the forthcoming Congress and the many events associated with an international meeting of this kind require that a fee be charged this year. The $25.00 fee entitles members to attend all scientific sessions, the opening reception, formal banquet and other social events planned for Congress delegates, and exhibits and special sightseeing tours to medical installations in Washington and its environs. Also included are the printed program, directory of registrants, Congressional badge and other items.

Associate membership (wives and family) has been arranged at a cost of $15.00. It will include all privileges mentioned above except the printed program. *A schedule of reduced fees has been provided for limited attendance by physicians and for attendance by such groups as medical students, interns, and nurses.*

Exhibits

Scientific and industrial exhibits have been planned for the Congress, as well as a motion picture program of professional and scientific films on cardiovascular subjects. Those wishing to present scientific exhibits or films should communicate with Charles D. Marple, M.D., Medical Director of the Association. Industrial firms interested in presenting an exhibit should communicate with the Exhibit Manager, Steven K. Herlitz, 280 Madison Avenue, New York 16.

Schedule

A tentative schedule of the Congress follows:

Saturday, Sept. 11, 5:00 to 10:00 p.m.: Registration, Mayflower Hotel

Sunday, Sept. 12:
9:00 a.m. to 10:00 p.m.: Registration, Mayflower Hotel
10:30 a.m.: Opening ceremonies at Constitution Hall
5:00 p.m.: Reception for Congress Members, Pan American Building

Monday, Sept. 13 through Friday, Sept. 17: Scientific Sessions at National Guard Armory.
Morning sessions will be held every day from 9:00 a.m. to 12:30 p.m.

Afternoon sessions will be held every day except Wednesday, Sept. 15 and Friday, Sept. 17, from 2:00 p.m. to 5:30 p.m. Sessions will be composed of round table and clinical pathologic conferences (panel discussions) in a large auditorium and presentation of scientific papers in four smaller section rooms.

onday, Sept. 13, 8:30 to 10:30 p.m.: Visit to National Gallery of Art, for Congress Members only.

Tuesday, Sept. 14, 8:00 p.m.: Formal banquet for Congress Members, to be held simultaneously at Mayflower and Statler Hotels.

Wednesday, Sept. 15, 2:30 to 5:30 p.m.: Medical sightseeing tours.

Thursday, Sept. 16, 8:30 p.m.: Special entertainment for Congress Members.

Friday, Sept. 17, 2:30 to 5:30 p.m.: Medical sightseeing tours.

SECTION ON CIRCULATION

The Section on Circulation of the Scientific Council is planning a special scientific session for members on matters of peripheral circulation as well as a general session to be held in connection with the Second World Congress of Cardiology in Washington, D. C., September 12–17. The exact dates of this Section's meeting will be announced later.

The Executive Committee of the Section on Circulation will meet on Monday evening, September 13. The Annual Dinner of the Section will be held on Wednesday evening, September 15, at the Shoreham Hotel. Additional details may be obtained from the Secretary, Grace M. Roth, Ph.D., Mayo Clinic, Rochester, Minn.

SECTION ON CLINICAL CARDIOLOGY

Over 2,000 doctors—the largest attendance at any medical meeting in the history of the American Heart Association—attended a two-day scientific program of the Association's Section on Clinical Cardiology held in Chicago on April 3–4 in conjunction with the Association's 30th Annual Meeting.

The printed program of the scientific meetings of the Section, containing abstracts of the papers presented and those read by title only, is available at 50 cents a copy. Copies may be obtained by writing to the Medical Director, Charles D. Marple, M.D.

Officers of the Section on Clinical Cardiology elected at a business meeting of the Section in Chicago include: Chairman, Emmet Bay, M.D., Chicago; Vice-Chairman, William P. Thompson, M.D., Los Angeles; Secretary, Hugh Hussey, M.D., Washington, D. C.

New members elected to the Executive Committee of the Section are: Wright Adams, M.D., Chicago; Francis F. Rosenbaum, M.D., Milwaukee; Edward Orgain, M.D., Durham, N. C.

PROCEEDINGS OF HIGH BLOOD PRESSURE RESEARCH MEETING

The Proceedings of the 1953 Annual Meeting of the Council for High Blood Pressure Research have been published as a cloth-bound, 96-page hard cover monograph which is available from the American Heart Association or Affiliated Heart Associations at $2.00 a copy. The book includes five reviews of recent original investigative work presented at the 1953 Annual Meeting of the Council held in Cleveland last May. It complies in one convenient reference volume material which otherwise is scattered throughout medical literature.

The authors are Drs. R. W. Sevy, Georges M. C. Masson, Simon Rodbard, D. M. Green and George A. Perera. The subjects covered include the relations between hypertension and the anterior pituitary, the adrenal cortex, renin, salt-water balance, sodium metabolism and electrolyte metabolism.

The 1953 Proceedings is the second volume in a projected series. The first volume, the Proceedings of the 1952 meeting, is still available at a cost of $1.75, paper-bound.

UNIVERSITY OF MINNESOTA SYMPOSIUM

The Proceedings of a symposium on recent advances in cardiovascular physiology and surgery presented last September at the University of Minnesota are now available at $1.00 a copy from the Minnesota Heart Association. The symposium was presented by the Minnesota Heart Association and the University of Minnesota. Copies may be obtained from Mr. G. Ray Higgins, Executive Secretary, Minnesota Heart Association, 542 Endicott-on-Fourth, St. Paul 1, Minn.

MEETINGS

June 14–18: Canadian Medical Association; Vancouver B. C.; T. C. Routley, M.D., General Secretary, 244 St. George Street, Toronto 5, Ont.

June 18–19: American Rheumatism Association; San Francisco; W. H. Kammerer, Secretary, 33 East 61st Street, New York 21.

June 19: International Society of Angiology; North American Chapter; Hotel Mark Hopkins, San Francisco, Calif., Dr. Henry Haimovici, Secretary, 105 East 90th Street, New York.

June 20: Society for Vascular Surgery; San Francisco; George D. Lilly, Secretary, 25 S. E. Second Avenue, Miami 32, Fla.

June 21–25: American Medical Association, Annual Meeting; San Francisco; Dr. George F. Lull, Secretary, 535 North Dearborn Street, Chicago 10, Ill.

July: South American Congress of Angiology; São Paulo, Brazil; Dr. Rubens Carlos Mayall, Rua Senador Vergueiro 73, Rio de Janeiro, Brazil, S. A.

July 9–10: European Society of Cardiovascular Surgery; Edinburgh, Scotland; A. J. Slessor, Department of Surgery, University New Building, Edinburgh 8, Scotland.

July 12–22: International Gerontological Congress; London and Oxford, England; Professor R. E. Tunbridge, President, General Infirmary, Department of Medicine, The University, Leeds, London.

July 20–24: International Conference on Thrombosis and Embolism; Basle, Switzerland; W. Merz, M.D., Honorary Secretary, Chief Medical Officer, Gynecological Clinic, University of Basle.

Aug. 9–13: National Medical Association; Washington, D. C., John T. Givens, Secretary, 1108 Church Street, Norfolk 10, Va.

Sept. 6: American Society of Clinical Pathologists, Washington, D. C.; C. G. Culbertson, Secretary, 1040 W. Michigan Street, Indianapolis, Ind.

Sept. 6–10: International Congress of Clinical Pathology; Washington, D. C. Dr. Robert A. Moore, Chairman, Committee on Arrangements, Washington University School of Medicine, St. Louis 10, Mo.

Sept. 6–11: Congress of Physical Medicine and Rehabilitation; Washington, D. C. Francis Baker, Secretary, One Tilton Avenue, San Mateo, Calif.

Sept. 9–10: Vermont Heart Association and University of Vermont College of Medicine Seminar on Cardiac Arrhythmias; Burlington, Vt.; E. Lepeschkin, M.D., University of Vermont College of Medicine, Burlington, Vt.

Sept. 11: Vermont Heart Association and University of Vermont College of Medicine Symposium on the U wave of the Electrocardiogram; Burlington, Vt., E. Lepeschkin, M.D., University of Vermont College of Medicine, Burlington, Vt.

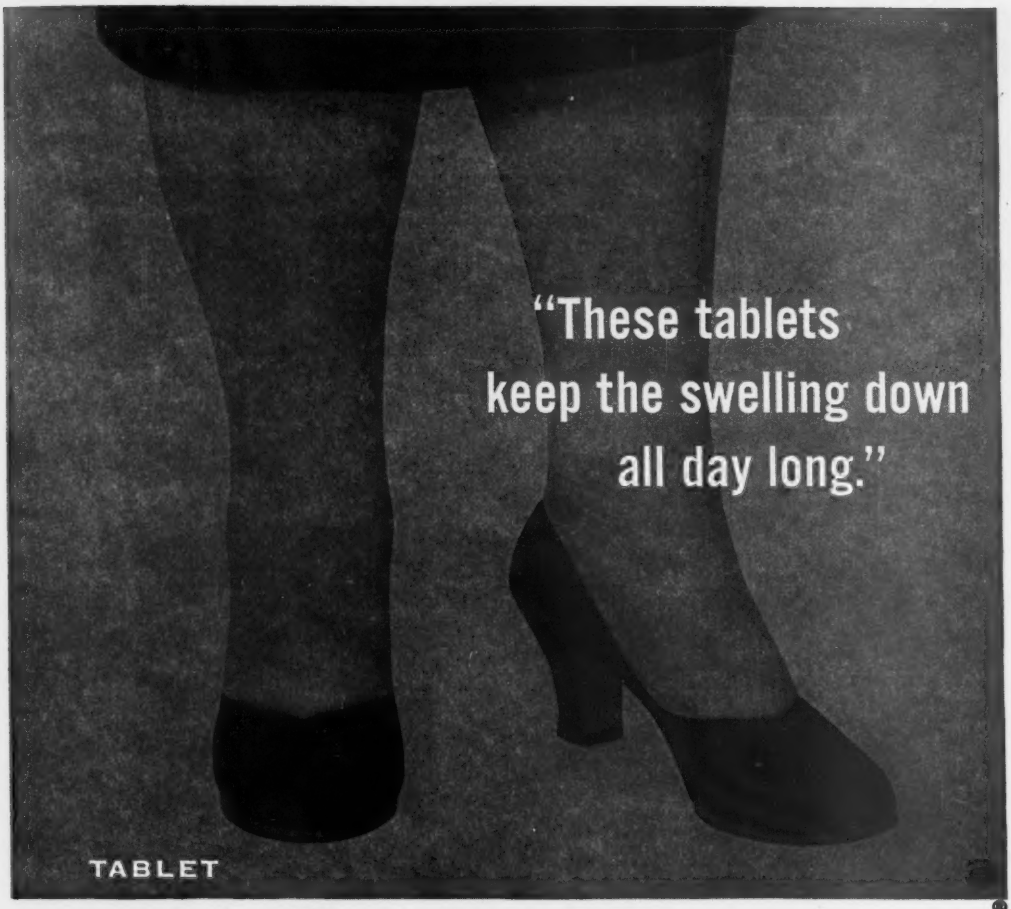
Sept. 12–17: Second World Congress of Cardiology and the 27th Annual Scientific Sessions of the American Heart Association; Washington, D. C. L. W. Gorham, M.D., Secretary-General, Care of the American Heart Association, 44 East 23rd Street, New York 10.

October 22–23: Annual Meeting and Scientific Program, Council for High Blood Pressure Research, American Heart Association, Cleveland. Irving S. Wright, M.D., Chairman, Program Committee, c/o American Heart Association, 44 East 23rd Street, New York 10.

October 31–Nov. 1: American Society for the Study of Arteriosclerosis, Annual Meeting; Sheraton Hotel, Chicago. Arthur C. Corcoran, M.D., Program Chairman, Cleveland Clinic, Cleveland, Ohio.

ASSOCIATION FELLOWSHIPS AND GRANTS

Applications for Research Fellowships and Established Investigatorships for the 1955–56 fiscal year must be received by Sept. 15, 1954. Applications for research grants-in-aid may be filed up to Dec. 1, 1954. Information and forms may be obtained from the Association's Medical Director.



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CONTENTS

INDEX ISSUE

ATRIAL SEPTAL DEFECT. CLINICAL AND PHYSIOLOGIC RESPONSE TO COMPLETE CLOSURE IN FIVE PATIENTS ..... *S. Gilbert Blount, Jr., Henry Swan, Goffredo Gensini, and Malcolm C. McCord* 801

THE CIRCULATION IN COLD ACCLIMATIZATION ..... *G. Malcolm Brown, G. S. Bird, T. J. Boag, L. M. Boag, J. D. Delahaye, J. E. Green, J. D. Hatcher, and John Page* 813

LONG-TERM ANTICOAGULANT THERAPY. FURTHER EXPERIENCES *John Tulloch and Irving S. Wright* 823

CARDIOVASCULAR ADAPTATIONS TO PROLONGED PHYSICAL EFFORT *George L. Beckner and Travis Winsor* 835

CIRCULATORY CHANGES IN ACUTE MYOCARDIAL INFARCTION *Robert P. Gilbert, Melvin Goldberg, and Joseph Griffin* 847

STOKES-ADAMS ATTACKS WITH SIMULTANEOUS AURICULAR AND VENTRICULAR STANDSTILL ..... *Naip Tuna and John W. Scott* 853

STOKES-ADAMS SEIZURES. CASE REPORT OF "PAROXYSMAL VENTRICULAR STANDSTILL" AND ITS PRODUCTION BY CAROTID SINUS PRESSURE ..... *Ford K. Hick* 857

PECULIARITIES OF THE AFRICAN'S ELECTROCARDIOGRAM AND THE CHANGES OBSERVED IN SERIAL STUDIES ..... *H. Grusin* 860

ELECTROCARDIOGRAPHIC LEADS. III. SYNTHESIS *Richard McFee and Franklin D. Johnston* 868

SURGICAL TREATMENT OF TRICUSPID STENOSIS ..... *Thomas J. E. O'Neill, O. Henry Janton, and Robert P. Glover* 881

FATAL MYOCARDIAL SARCOIDOSIS ..... *J. D. Stephen* 886

INDICATOR-DILUTION CURVES IN ACYANOTIC CONGENITAL HEART DISEASE *James C. Broadbent and Earl H. Wood* 890

ROLE OF ARTERIAL WALL SECRETION IN THE REGULATION OF BLOOD PRESSURE *C. Jiménez Diaz, P. Barreda, A. F. Molina, and R. Alcalá* 903

AURICULAR FIBRILLATION AND MITRAL STENOSIS IN BACTERIAL ENDOCARDITIS *Jacques B. Wallach, Macellis Glass, Leslie Lukash, and Alfred A. Angrist* 908

A MORPHOLOGIC STUDY OF CANINE HEARTS SUBJECTED TO FIBRILLATION, ELECTRICAL DEFIBRILLATION AND MANUAL COMPRESSION *C. G. Tedeschi and C. W. White, Jr.* 916

CLINICAL PROGRESS. CARDIOVASCULAR PROBLEMS IN PREGNANCY *Burton E. Hamilton* 922

ABSTRACTS 934

AMERICAN HEART ASSOCIATION 957